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Investigations into the Transit of Ova in Man*

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INTRODUCTION

DESPITE numerous investigations into the anatomy and physiology of the adnexa, one has as yet failed to arrive at a clear understanding as to how the ovum in man set free from the ovary is transferred to the Fallopian tube.

Since for obvious reasons it is impossible to carry out any direct observations of this stage of the ovular transit in man, one has had to be content with analogous conclusions from observations on animals. By a closer study of the anatomical structures of the female pelvis, especially the course of the smooth musculature of the adnexa and of the peritoneal folds by means of which the adnexa are attached, one has also tried to surmise the likely relative position of the organs at the moment of ovulation.

In this manner Rouget tackled the problem in a work published in 1858. Rouget[1] draws attention to the presence of plenty of smooth musculature in the ovarian ligaments in man. From the uterine horn muscular fibres radiate and accumulate into the lig. ovarii proprium. This ligament is attached to the uterine pole of the ovary, but some of the muscle fibres cross the hilus ovarii to reach the upper pole of the ovary and spread to the ovario-fimbrial ligament.

The presence of smooth musculature can also be ascertained in lig. suspensorium ovarii. Here the muscular bands mainly

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pass parallel with the ovarian blood-vessels. Some of the muscle fibres spread into the ovary at the hilus, others pass to the uterus, while others again proceed to the pars ampullaris of the Fallopian tube. By alternating contractions of the musculature concerned, Rouget has conceived the idea that the tube and mesosalpinx on ovulation may sweep round the ovary whereby this becomes more or less completely enclosed in a peritoneal pocket or bursa, at the same time as the infundibulum is dragged down over the surface of the ovary. In such circumstances the distance the ovum would have to pass from the ovary to the tube would be quite short.

The chief point in Rouget's deduction is, therefore, that although a closed bursa ovaria does not exist in man, a structure of that nature is nevertheless formed at the moment of ovulation whereby the ova are prevented from getting lost in the general peritoneal cavity. Rouget has not submitted any experimental proofs of the validity of his theory.

Several authors of the older school, especially Aeby,[2] have shared Rouget's view, yet it has always been said that a fully closed ovarian bursa cannot conceivably arise, at any rate not for good, since in such circumstances a transperitoneal passage of the ovum would be out of the question.

In the literature of recent years dealing with the anatomy and physiology of the adnexa there is little or nothing to impart to us the ideas of the old school as referred to above. The transit of the ovum from the ovary to the Fallopian tube is generally stated to be due to the ciliary current assumed to exist in the tube. Through such current the ova emitted into the abdominal cavity and lying about there by themselves are supposed to be sucked into the tube.

A fluid current in the tube, as also a sucking movement towards the ostium abdominale, can experimentally be proved to exist. If indian ink be injected into the peritoneal cavity of experimental animals, ink granules can be shown after a relatively short interval to be present in the tube. The same thing is borne out by investigations that used to be carried out in cases of human sterility in which some dye, injected into the pouch of Douglas was subsequently proved to be present in the vagina while the tubes were open. The transperitoneal transit of the ova also clearly indicates the same thing.

Whether the current, however, is really produced by the cilia, or at any rate mainly so, may be open to discussion, because the fact is that cilia and secretory cells occur alternately

in the tube. Such periodical alternation is very easy to observe in some animal species. It was thus shown by Sobotta[3] on mice that in these animals during ovulation there did not exist any cilia, the mucous membrane of the tube being entirely covered with secretory epithelium. It must seem highly irrational were the cilia to disappear completely at the very time when they are most in need, provided it is true that the ciliary current is of such great importance for transporting the ovum.

Such periodical alternation in the relative existence of secretory and ciliary cells can also be observed in all other animal species subjected to examination, as also in man, even if the alternations here are not so obvious.

Even if the ciliary cells do not play any decisive part in the production of the tubal current other forces exist, however, which may be considered as productive of a suction and current effect. The wall of the Fallopian tube contains smooth musculature, circular as well as longitudinal. Investigations by Kok,[4] v. Miculicz-Radecki,[5] Dyroff[6] and others have shown this musculature to be the seat of rhythmic contractions, and for my own part I have been able to make a precise study of this muscular activity *in vivo* in rabbits, as also in monkeys, including a record of its rhythm. The different investigations have made it clear that the muscular activity concerned is hormonally regulated. It is most pronounced in connexion with follicular maturation and the rhythmic contractile waves, directed towards the uterus, undoubtedly produce a powerful suction within the tube.

Even if the tubal suction is sufficient to carry with it particles located in the general peritoneal cavity, certain protective mechanisms exist which are likely to safeguard still further the transit of the ovum from ovary to tube.

In some mammals, such as mice and rats, the transit just mentioned is effectively safeguarded by the ovary being enclosed in a peritoneal capsule, into which the tube opens. Ova becoming loose from the ovary float about in the fluid in the capsule, and when the tube exercises its suction effect the ovum will promptly be carried into it. There is no chance here of the ova getting lost in the abdominal cavity.

Things are different in the higher animals in which there is no anatomically closed bursa. However, the idea has been advanced that a functionally closed bursa might form here as a result of the tube's, with its mesosalpinx, curving round the ovary and enclosing it.

With the view to getting a closer knowledge of the subject I carried out, as earlier related, direct observations of the adnexa in rabbits by the aid of an abdominal window. In the rabbit the Fallopian tube does not run, as in man, in the free border of the lig. latum. The result of this is that we are able to recognize a mesotubarium inferius, by which the tube is attached to the posterior abdominal wall, and a mesotubarium superius extending as a thin membrane between the two parts of the cranially convexly curved tube, of which the medial, relatively short part ends in the ostium abdominale, while the lateral continues down to the uterus. The mesotubarium sup. terminates into a caudomedially directed free border, along which the fimbriae extend. Because of the curved shape of the tube the two mesotubaria form a peritoneal pocket round the ovary.

It was formerly assumed that the pocket or bursa just mentioned was functionally closed at the ovulation periods as a result of the two tubal parts approaching one another. In this way the ovary would become entirely enclosed in the bursa and the ova prevented from escaping into the general peritoneal cavity. Such, however, is not in accordance with fact, since by observations made through an abdominal window during ovulation the following phenomena came to light. The entire tube is drawn rhythmically down to the uterus, the two tubal parts approach one another and the free border of the mesotubarium superius becomes taut, which means that the fimbriae, being attached along the border, spread out. (See Fig. 1.) Displacement of the tube is explained by contractions of the smooth musculature, of which there is a great quantity in the mesotubarium inferius and which runs parallel with the tube. On the contraction relaxing the tube glides back to its initial position. During oestrus the contractions appear regularly at intervals of 7 to 20 seconds. For each contraction the fimbriae, extended along the free border of the mesotubarium, are dragged across the ovary, the same thing happening likewise when the contraction relaxes.

It is clear, therefore, that the ovary is not continuously enclosed in the bursa. Such is only the case when the contraction of the mesotubarium is at its maximum. So soon as it relaxes the ovary is lying more or less free in the abdominal cavity. (See Fig. 2.) But the main point is that the fimbriae are dragged to and fro across the ovary on contraction of the mesotubarium.

Yet another interesting observation could be made during oestrus. Instead of remaining immobile, the ovary was seen to shift its position cranially and caudally, due to rhythmic con-

tractions of the muscular ovarian ligaments, at the same time as it rotated round its long axis, causing now the one then the other of its surfaces to face the fimbriae and the ostium abdominale.

By the extremely ingenious mechanism here described, and set in function during ovulation, this much is attained—that the infundibulum is continuously carried to and fro over the ovary, which in the meanwhile exposes its different surfaces.

In the tube itself a lively muscular activity could simultaneously be observed with powerful contractions directed towards the uterus.

Under such exceedingly favourable conditions there is every likelihood of the ova being sucked directly into the tube. Most likely the ova never reach either a bursa or, still less, the general peritoneal cavity, but are conveyed directly from the ovary to the tube.

During non-oestral periods the contractions of the mesotubarial muscles are found to be weak, and appear at long and irregular intervals. On the whole, movements of the ovary were not to be seen. Peristalsis of the musculature of the tube is definitely weaker than during oestrus.

Having succeeded by observations through an abdominal window in forming an opinion as to what forces are set in motion in the rabbit to provide for ovular transit, it seemed to me of great interest also to carry out similar investigations in higher animals, the anatomical characters of which were more in accordance with those of man. To that end I[8] selected as experimental animals *Macacus rhesus* monkeys. Since it was impossible to make an abdominal window here, observations were instead carried out through a laparoscope.

The anatomy of the adnexa in *Macacus rhesus* is fairly like that of man. Although the whole tube does not run in the free border of the lig. latum it passes very close to it. In that way a small ovarian bursa is formed, but it is not large enough to enclose the entire ovary.

With the exclusion of all details, the following observations were made through the laparoscope during different phases of the sexual cycle. During the inter-oestrual periods the tube takes the shape of a laterally convex curve and is moderately twisted. The ovary is, on the whole, lying free and is available for direct inspection. During oestrus the tube is found strongly twisted and bow-shaped, so much so that the pars ampullaris and the pars isthmica approach one another. (See Fig. 3.) Thereby the infundibulum is turned round and faces the ovary. During

the whole of the oestrual period the tube retains this position; only minor movements may be observed by which the fimbriae are regularly dragged to and fro over the ovary. It was striking to note that the fimbriae during the periods concerned were strongly hyperaemic and extended, and at times the infundibulum covered the whole ovary.

As in the rabbit an auto-motion of the ovary can also be observed in *Macacus*, including minor displacements in a cranial and caudal direction, as well as rotary movements round the long axis. In this way the different ovarian surfaces are exposed to the infundibulum.

The movements of the Fallopian tube and ovary are caused by smooth musculature embedded in the mesotubarium and in the ovarian ligaments. The anatomy of this musculature I have described in detail in my earlier work.

The tube itself is the seat of contractions mostly directed towards the uterus; during the oestrual period they are exceedingly powerful and follow one after the other in rapid succession.

In comparing the two animal species, rabbit and *Macacus rhesus*, we find, in spite of the relatively dissimilar anatomical conditions, a principal likeness in the fact that the ostium abdominale of the tube with surrounding fimbriae, thanks to contractions of the mesotubarial musculature, is brought to and fro across the ovary, which itself rotates on its long axis, whereby its different surfaces are exposed.

In view of this, it may readily be assumed that the mechanism of the ovular transit in man is of similar nature, the more since there is much analogy in anatomical respect between the monkey and man.

By experiments *in vitro*, as well as by observations at operations, the human Fallopian tube has been found to be the seat of muscular peristalsis. Thanks to this peristalsis and the activity of the cilia, a powerful current is set up through the tube. Foreign bodies (indian ink and such like) injected into the abdominal cavity are carried away by this current and are transferred, as already mentioned, through the tube and uterus to the vagina.

The question, however, as to how the ovum is transferred from the ovary to the tube has given rise to much discussion. As indicated, earlier authors of the old school held that the tube on ovulation approaches the ovary. This idea was subsequently, however, discounted, and instead it was believed that the ova enter the general abdominal cavity and, thanks to intestinal

peristalsis, force of gravity and the like, are brought down to the pouch of Douglas. Since there is a certain amount of fluid here in connexion with the ovulation, the ova would be suspended in this and so readily be sucked up by the tube, which on these occasions would lower its ampullary portion down towards the floor of the pouch of Douglas.

v. Miculicz-Radecki[5] has advanced another solution of the problem. When operating on women with healthy genital organs in connexion with sterilization, he studied in detail the position of the Fallopian tube in different stages of the menstrual cycle, and in consequence he advanced the following theory. Prior to sexual maturity the tube is not in contact with the ovary. The ampulla and the infundibulum are located on the lateral side of the upper pole of the ovary. As ovulation begins, the relative position of tube and ovary becomes periodically altered. On rupture of the follicle the pars ampullaris enlarges from hyperaemia and, as a result of increased weight and altered tone in the musculature of the mesosalpinx, descends along the medial surface of the ovary whereby the fimbriae come in contact with its lower pole. Through contractions of the pars isthmica, the pars ampullaris and the mesosalpinx are drawn across the ovary like a curtain, which causes the ovary to become enclosed in a peritoneal pocket.

On ovulation the ovum enters this pocket and is sucked up from it by the tube. Purely functionally there thus exists, in fact, a bursa ovarica mechanism. The ovum will never come out into the general peritoneal cavity.

Without denying that such bursa formation may be of some importance one can scarcely, however, ascribe to it, as v. Miculicz-Radecki has done, such decisive claims of being a protective device during ovular transit. In the first place, it must be remembered that not even in animals, such as rabbits, in which a fully closed bursa can form, which is not the case in man, is the ovary continuously enclosed in the bursa on ovulation. Secondly, it has been established by a number of observers that ova from the ovary of one side may be brought across to the tube on the other.

In such circumstances it must be assumed that other arrangements exist for safeguarding the transit of the ovum.

In the literature of recent years the old idea of the tube actively approaching the ovary and spreading its fimbriae over its surface has again been revived. Thus Caffier[9] describes some observations made at operations performed at the time of ovula-

tion and when the patients had been prepared with prolan. He found the tube curving round the ovary in a bow-shaped manner and the fimbriae spreading out over it, and of particular interest is that in one patient the tube of one side extended across to the ovary of the other, enclosing it with its infundibulum.

Conclusions regarding the ovular transit have been drawn from observations of the position of human adnexa as found at operations. All such observations have this in common, that they merely give us the picture of a temporary position, such as found at the time of operation, but they do not give us any definite idea of what movements the organs are capable. There can be no doubt, however, that the tube is able to change its position very considerably, nor can it be questioned that this change in position must be due to some muscular activity in the organ itself. The possibility of the ovary having its own power of mobility, as was the case with the experimental animals examined by me, has, on the whole, never been discussed.

Method and Material.

In the investigation to be described below I have tried to analyse more closely the mechanism of ovular transit in man. The starting-point was a belief that it should be possible by X-ray examinations of the internal genital organs to get some information as to their anatomical interrelation and of the displacement which may occur during different phases of their function. The position of the tube in different situations can be established by the aid of salpingography. In ordinary circumstances the ovary is as little visible on the radiogram as the tube. To enable observations to be made on the ovary, however, I adopted the following method. On the abdomen being opened, for instance, when operating for a unilateral ovarian tumour or chronic appendicitis, I inject by a fine needle a drop of lipiodol under the tunica albuginea of the ovary at the upper as well as the lower pole and perhaps also in the free border. By these small indicators, which are gradually absorbed and little by little entirely disappear, I have been able, on subsequent Roentgen examination a short time after the operation, to obtain a clear view of the position of the ovary in the pelvis. By taking a few serial films one is able to ascertain whether the indicators have in any way altered their positions, as also the relation of the ovary to a dye-filled tube.

For the great assistance I have received during the Roentgen examinations from the heads of the Roentgen Departments of

Uppsala and Lund, Professor H. Laurell and Dr. H. Hellmer, I wish to extend my sincere thanks.

Naturally, to be able to interpret Roentgenograms taken in the above-mentioned manner, it is essential to be fully familiar with the normal topographical anatomy of the adnexa. Moreover, should the relatively well-marked displacements of the adnexa during ovulation, observed in the experimental animals, have any analogy in man, we must conclude also here the presence of smooth musculature in the suspensory apparatus of the organs as is the case in animals.

The normal position of the ovary has been very differently described by various authors. In current textbook literature, I suppose, the description given by Hammerschlag[10] is the most prevalent. According to this author the ovary is suspended between the ligamentum suspensorium ovarii passing upwards and outwards and the lig. ovarii proprium going to the uterus. The hilus area where the ovary is attached to the mesovarium, a fold of the posterior layers of the lig. latum, is directed forwards and outwards and the free border of the ovary backwards and inwards. One of the ovarian surfaces is in contact with the pelvic wall, where sometimes may be found a shallow depression, "fossa ovarica". The longitudinal axis of the ovary is nearly vertical.

As already mentioned, the description given of the position of the ovary by different authors has greatly varied. In illustration a few examples may suffice. Schultze has found that the hilus faces downwards and the margo libra upwards, while Koelliker states that the ovary may so turn on itself that the free border faces downwards, and Schauta[11] holds that this is the normal position of the ovary. Martin,[12] who has made a very close study of the topographical anatomy of the ovary, shares Hammerschlag's opinion, but strongly emphasizes that its position is greatly influenced by the character of the mesovarium. In the case of this being long, the ovary will be very mobile, and if it is short the contrary will apply.

Such different views as to the topography of the ovary must, in part, be due to different methods of examination, individual variations, and different length of the mesovarium. A factor, however, which has been altogether overlooked, but which undoubtedly is also of great importance, is that the position of the ovary must largely become influenced by the different states of tension of the ovarian ligaments, a thing which will be more closely dealt with in what follows.

The ovary is, as expressed by Hammerschlag, " suspended " between the ligamentum suspensorium ovarii and lig. ovarii proprium. In lig. suspensorium are found ovarian vessels and nerves, but beyond this it is stated in current anatomical literature that the ligament merely contains connective tissue and fat. Lig. ovarii proprium contains plenty of connective tissue besides smooth musculature radiating from the uterus.

The smooth musculature of the ovarian ligaments has attracted surprisingly small interest. As already mentioned, it is really only Rouget and Aeby, and in more recent times and more closely Wallart,[13, 14] who have devoted any attention to the question. This author states that even in the child smooth musculature exists round the hilus ovarii. In the adult woman it may be observed how the musculature forms a subserous layer underneath the two peritoneal folds in the mesovarium. Moreover we find here intervascular muscle fibres spreading into the hilus and into the ovarian marrow. These fibres run mainly parallel with the vessels, but sometimes they separate and curve round the vessels.

It is quite simple to verify Wallart's observations. The mesovarium holds a great quantity of smooth musculature. On closer study, however, it can be found to exist, not only in the ovary and mesovarium, but also extending far beyond these organs.

I have made serial sections through the suspensory apparatus of the ovary from the upper attachment of the lig. suspensorium down to the uterus, and below will be found the deductions made from the microscopical slides.

From its origin down to the ovary the lig. suspensorium contains numerous strands of smooth musculature scattered between the blood-vessels and running mainly parallel with these. In addition to these, however, it is of great interest to note that the adventitia of the veins is of enormous thickness because of the great quantity of longitudinal musculature embedded in it. (See Figs. 4 and 5.) There can be no doubt that contractions of the vascular and intervascular longitudinal musculature should be able to create considerable variations in the tension of the lig. suspensorium ovarii.

As earlier described, there are also plenty of longitudinal muscular fibres in the lig. ovarium proprium. In such circumstances the ovary will be suspended in bands which, on account of varying states of contraction in the embedded muscu-

lature, can be shortened or elongated, and this must greatly influence the position of the ovary in the pelvis.

The tuba uterina begins at the uterine horn and, according to current anatomical descriptions, it runs in a transverse direction towards the pelvic wall, continuing afterwards in a bow-shaped manner backwards and upwards round the lateral surface of the ovary. In some cases it is found to take a straighter course upwards, and in such circumstances the fimbriae cannot have any direct contact with the ovary. In other cases again, it curves round the upper pole of the ovary, whereby the fimbriae, to a greater or lesser extent, come to be in contact with the medial surface of the ovary. (See Fig. 6.) Like the tube, the mesosalpinx is also bent in a bow-shaped manner. In this way we get an indication of a bursa ovaria in which, however, the ovary is by no means entirely enclosed.

Contrary to the lower animals there is a very sparing amount of smooth musculature in the mesosalpinx of man. Individual fibres pass in various directions, mostly however parallel with the tube, but the active movements of which the tube undoubtedly is capable, must above all be the outcome of contractions of the musculature present in its walls.

There is every reason to assume that the smooth musculature present in the suspensory apparatus of the adnexa in man has a definite mission to fulfil, chiefly then in the form of shifting their relative positions. The observations made at the Roentgen examinations to be described below also confirm that such is the case.

Case 1. Aged 38. Last menstruation 1st October, 1935. Operation performed 5th October when a right-sided ovarian cyst was extirpated. In the upper pole of the normal left ovary a drop of lipiodol was deposited and about 1 cm. lower down another one. *Roentgen examination* 20th October. The lipiodol drops visible on the screen were focused in a slit-shaped diaphragm. Serial exposure at 4-minute intervals.

During the first 12 minutes the lipiodol drops were found to be lying perfectly still but after that they were shifted somewhat caudally. At the 5–7 exposures they had moved about 10 mm. upwards and subsequently they again descended a little during the following exposures. In the course of examination, therefore, the upper pole of the ovary had been displaced upwards as well as downwards, clearly in evidence on the serial film by a wave-like motion of the lipiodol drops. (See Fig. 7.) *The examination thus shows that the ovary has shifted alternately in a cranial as well as caudal direction.*

Case 2. Aged 16. Last menstruation 19th October, 1936. Operation performed 9th December for right-sided tubal pregnancy. Salpingectomy

on right side. In the normal left ovary 3 lipiodol drops were deposited, one at each pole and one at the middle of the margo libra. No bleeding occurred after the operation. *Roentgen examination* 28th December.—In the course of 40 minutes 10 films were taken at 4-minute intervals between the exposures.

On the first film the lipiodol drops in the lower pole and on the free border appear as isolated shadows while the drop deposited in the upper pole has split into two. A few minute drops can also be seen scattered about here and there due to some lipiodol having escaped into the abdominal cavity at the time of operation.

In the course of the first 12 minutes from the onset of examination the ovary moved about 14 mm. in a cranial direction. At first, however, the relative position of the lipiodol drops remained unaltered. Between the 3–5 exposures the ovary rotated in such a way that the upper drop, split into two halves, became covered by that located in the free border (see Figs. 8 and 9) but on the 7th film it began to reappear and on the 10th exposure it had resumed its original position. In the course of the examination the whole ovary was displaced in a cranial direction, being located about 20 mm. higher at the end of the examination than at its start.

The examination thus shows that the ovary had changed its position and this in two different ways. In the first place it had been displaced for a considerable distance upwards, secondly it had rotated to and fro on a long axis, as evidenced by the change in the relative position of the indicators.

Case 3. Aged 32. Last menstruation 28th August, 1936. Oöphorectomy was performed 3rd September, 1936, for left-sided ovarian cyst. In the right normal ovary lipiodol drops were deposited, 1 in the lower pole and 2 in the upper. *Roentgen examination* 16th September.—The examination went on for 44 minutes, exposures being made every 4th minute. Before the onset of examination a salpingography instrumentarium was inserted.

On the first plate the 3 lipiodol drops were seen as shadows, the size of peppercorns. Those deposited in the upper pole were located about 20 mm. below the right ilio-sacral articulation, and that in the lower pole about 40 mm. below this joint and situated further medially than the other one. After 4 minutes the drops had exactly the same position as at the first exposure. After another 4 minutes they had shifted 3 mm. caudally. After 12 minutes from the start they had resumed their original position. After 16 minutes they had moved 25 mm. upwards and at the same time somewhat laterally. At this stage 4½ c.c. of lipiodol were injected into the uterus. The cavum uteri and tubes were well filled; 20 minutes from the start of examination the drops had risen another 4 mm. On this film the contrast in the fimbrial end of the tube can be seen to be projected just above the upper pole of the ovary (see Fig. 10). After 24 minutes the drops had risen 4 mm. and after 28 minutes a very marked displacement of no less than 9 mm. had taken place in a direction upwards

and simultaneously also laterally. The upper ovarian pole, earlier projected below the linea terminalis, was now located above it. The abdominal ostium was now seen to be lying close to the upper pole of the ovary (see Fig. 11). After 32 minutes the ovary had been displaced upwards for 16 mm. (see Fig. 12), and after 36 minutes another 20 mm. The abdominal ostium of the tube was now located at the lower ovarian pole (see Fig. 13). Finally after 44 minutes the drops had again been displaced in a caudal direction.

It is clear, therefore, that the examination had revealed considerable changes in the position of the ovary. To start with the ovary had descended a little and then slowly shifted upwards for a distance of no less than 81 mm. altogether and at the same time laterally nearly 40 mm. After this there was finally a movement in a caudal direction.

It is of interest to note that the gas bubble in the gut as well as the contour of the urinary bladder are very clearly defined on the films. The gas bubble does not shift during the examination. The bladder filled up at first, and the outline rose in the course of the first 24 minutes, but afterwards the contour is seen to remain at exactly the same level in the pelvis. This, therefore, constitutes an excellent piece of evidence, showing that the great changes in the position of the ovary occurring at this very stage have nothing to do with the different states of filling of the bladder or intestine.

The examination has thus shown a very considerable ovarian displacement in a cranio-lateral direction. Simultaneous salpingography revealed that the abdominal ostium of the tube altered its position in relation to the ovary. From being located at first above the upper ovarian pole the ostium was found at the lower ovarian pole at the end of the examination.

Besides these 3 cases described in detail I have with the same technique studied 6 other cases. In 4 of these it was possible to prove ovarian movements of the same type as in the 3 first mentioned. In 2 cases, however, the ovary remained immobile during the examination.

Discussion.

In reviewing the results obtained in the different examinations we find that in several cases we were able to demonstrate a definite alteration in the position of the ovary, and in some cases we have managed, thanks to simultaneous salpingography, to get a good idea of the relative anatomical position of the Fallopian tube and ovary.

The possible errors which must be taken into consideration in these tests have been, so far as it is possible to judge, entirely eliminated. The most important of these is naturally a change

of the patient's position in relation to the Roentgen tube in the course of examination, with consequent altered projection of the indicators. A check against this event was obtained by carefully comparing from film to film the projections of the different skeletal parts.

Another contingency that must be reckoned with is that the ovaries may become displaced because of varying amounts of contents in the bladder and intestine. In order to avoid this the intestine has been properly emptied prior to the examination, and in several cases a catheter *à demeure* has been left in during the examination. In Case 3, when such precautions were not taken, the different degree of filling of the bladder can be distinctly seen in the serial pictures by the contour of the bladder being clearly defined. It was found, however (for particulars see the clinical history of the case) that on those occasions when bigger displacements of the ovaries were observed there was no change in the position of the bladder's outline. At the same examination one could also see that the gas-bubble in the gut was located as before. In such circumstances we are justified in concluding that the altered position of the ovary is not caused by displacement of other organs.

We must finally ask ourselves whether in those cases in which salpingography was carried out this operation in itself might have altered the position of the ovaries either mechanically or by some reflex action. As evidence against this we find in one case that the ovary during the whole examination lay perfectly still although the uterus and tubes were filled with contrast.

The changes observed in the position of the ovaries vary in the different cases. Sometimes, as in Case 1, there is only a mild displacement both in cranial and caudal direction. In Case 2 we find a more pronounced shifting in a cranial direction and, in addition, there are signs of a very definite rotation of the ovary on a long axis parallel with the longitudinal axis of the ovary. In Case 3 the displacement is very considerable, amounting to no less than 88 mm. cranially and 40 mm. in a lateral direction. The measurements submitted are calculated to give the true displacement of the ovary in the pelvis.

Thanks to simultaneous salpingography one was able to make some interesting observations of the anatomical position of the ovary and tube. Thus in Case 3 we find that the ostium abdominale of the tube is at first projected over the upper pole of the ovary while towards the end of the examination it comes to lie over the uterine pole. In one case the tube was sweeping

round the ovary in a bow-shaped manner and in one other the contrast pouring out of the tube was flowing out over the ovary.

Various attempts to influence the ovarian movements by certain drugs, such as ergotoxin, adrenalin and atropin, and, hormonally, with oestrin have all failed to produce any results. Nor is it possible from the limited material concerned to draw any definite conclusions as to whether the ovarian movements vary in magnitude during different phases of the sexual cycle. This is probably the case, however, since in animal experiments referred to earlier it was found that ovarian movements chiefly took place during the periods of ovulation. It stands to reason then that in man, too, the more significant changes in the position of the ovary should occur in connexion with follicular maturity.

In the light of earlier observations of the mobility of the tube and ovary in rabbits and monkeys, and after analysis of the cases described above, it would seem possible to arrive at a well-founded understanding of the mode of transit of the ovum in man. This is how I think it happens. The tube which during sexually inactive periods is lying more or less straight (see Fig. 14, upper picture) curves round the upper pole of the ovary during ovulation in a bow-shaped manner. By that means the ostium abdominale with surrounding fimbriae will come to face the ovary (see Fig. 14, middle picture). The ovary will now perform movements of its own, upwards and downwards, as also in the form of rotation on a longitudinal axis (see Fig. 14, lower picture). The first-mentioned movements are due to alternating contractions of the smooth musculature contained, as already mentioned, in the lig. suspensorium ovarii as well as in the lig. ovarii proprium. As the first of these ligaments passes in a direction from above outwards to below inwards, it follows as a natural consequence that contractions in the muscular elements of the ligament must lead to the ovary being drawn upwards and laterally, which, in fact, as proved by the radiograms, is also the case.

If at the beginning of such an upward movement the ostium abdominale of the tube should be level with the upper ovarian pole, the ostium will necessarily, on account of the relative fixation occasioned by the ovario-fimbrial ligament, be turned against the ovary on this being elevated. In such circumstances the fimbriae will at first spread out over the upper part of the ovary, but the higher the ovary rises, the more will the fimbriae be disposed over the uterine pole of the ovary. Since, moreover,

the ovary can rotate on a longitudinal axis, because of certain parts of the smooth musculature taking a more or less spiral course, all conditions are fulfilled to enable the ovarian surfaces to be alternately turned against the tubal infundibulum.

It would seem, therefore, that principally the same mechanism is in operation in man as has been observed in the lower animals. The transit of the ovum is assured by the tube and ovary coming in intimate contact with one another on ovulation, and this is rendered possible, partly by the tube's own movements, partly by change in position and rotatory movements of the ovary.

At laparotomies performed about half-way between two menstrual periods several workers have observed, as already mentioned, that the fimbriae on these very occasions are strongly hyperaemic. This seems to indicate the presence of certain circulatory changes in the adnexa at the time of ovulation. Similar findings were made in the animal experiments. In monkeys the fimbriae were found during oestrus to be greatly distended and flushed which means that on ovulation they can practically cover the whole of the ovary. This capacity of the fimbriae to swell up and spread out over relatively large surfaces enables the rupturing follicle to become entirely covered by the infundibulum whereby a still further safeguard is obtained that the ovum shall be directly brought into the tube.

The hyperaemia and stasis of the fimbriae are probably brought about by the altered state of contraction of the musculature of the ligaments. Some of the muscle fibres are annularly arranged around the vessels wherefore on these fibres contracting the blood outflow must be hindered.

There is no doubt that the muscular adventitia of the veins of the lig. suspensorum aids the ovary in altering its position, yet it is quite possible that the musculature in question also has other missions to fulfil. Thus, for example, there is a great deal to be said in favour of the altered circulation and pressure conditions in the ovary contributing to the event of follicular rupture. Further, as we find a certain likeness in the anatomical construction of the ovarian veins and those of suprarenal glands, the adventitia in both types of vein being rich in muscular fibres, the idea immediately suggests itself that the musculature of the ovarian veins may also have another object, viz. to regulate the transport of the hormone from the ovary, in analogy with what is assumed to be the case concerning the regulation of the adrenalin transport from the suprarenal glands.

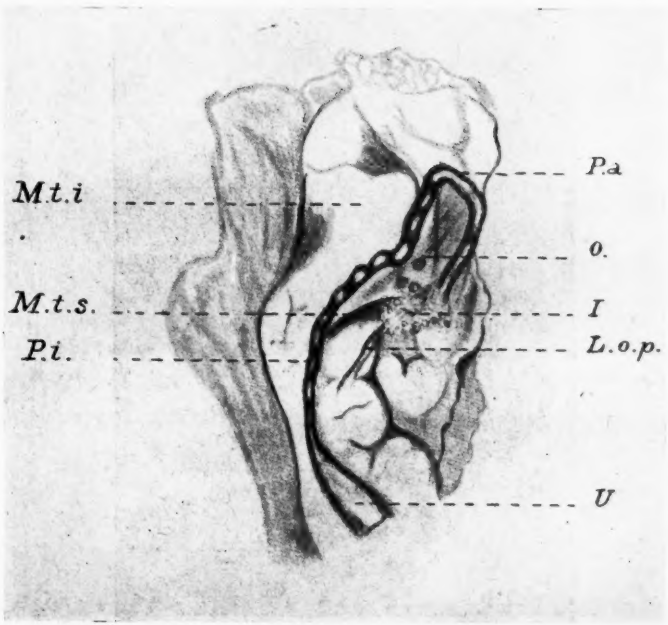

FIG. 1.

Adnexa on right side in a rabbit on maximal contraction of mesotubarial musculature. Ovary enclosed in bursa ovaria. Fimbriae extended. M.t.i. = Mesotubarium inferius. M.t.s. = Mesotubarium superius with its free border. I. = Infundibulum. Pa. = pars ampullaris tubae. P.i. = pars isthmica tubae. O. = ovary in the bursa. L.o.p. = ligamentum ovarii proprium. U. = uterus.

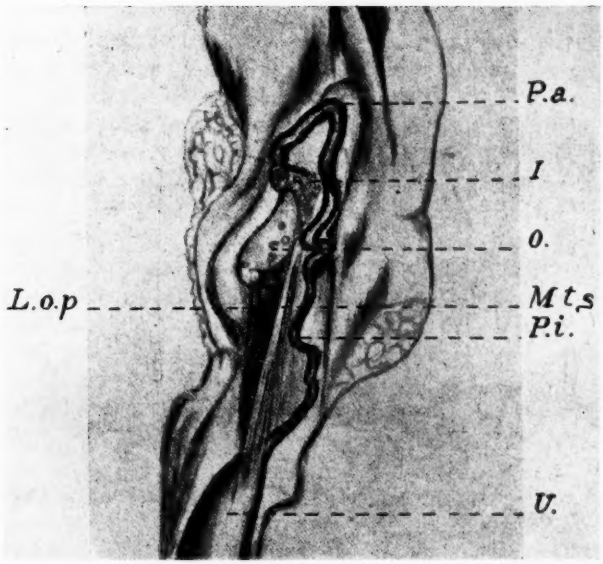

FIG. 2.

Adnexa on right side in a rabbit. Complete relaxation of mesotubarial musculature. Ovary outside bursa. Same signs as in Fig. 1.

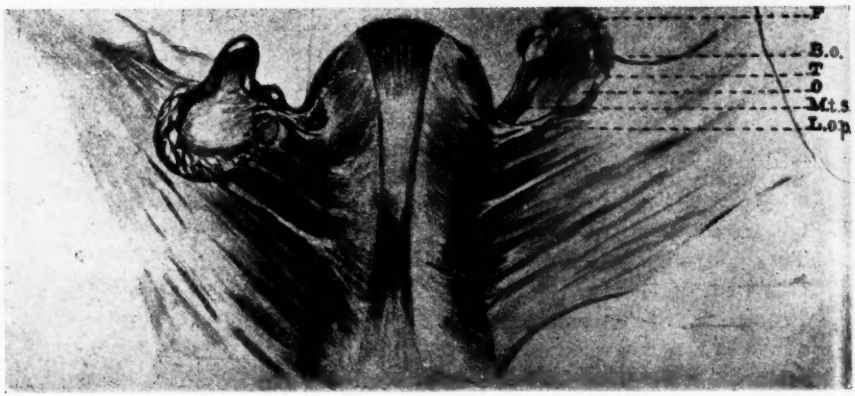

FIG. 3.

Uterus and adnexa in *Macacus rhesus*. Right ovary free. On left side tube bent over ovary. F. = fimbriae. B.o. = bursa ovaria. T. = tube. O. = ovary. M.t.s. = mesotubarium superius. L.o.p. = lig. ovarii proprium.

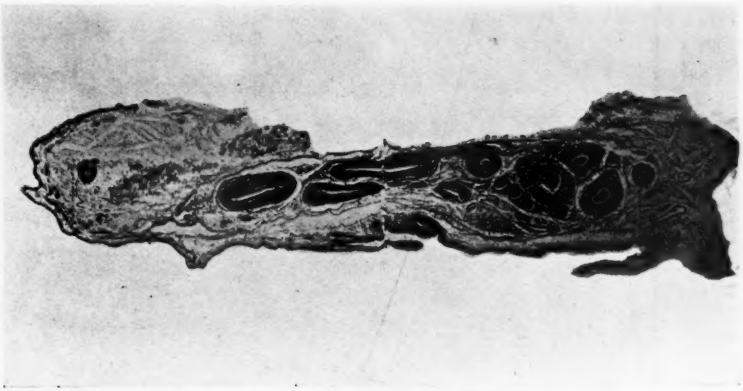

FIG. 4.

Microscopic transverse section of lig. suspensorium ovarii in man.

FIG. 5.

Detail from Fig. 4 in greater magnification. Observe the cross-cut smooth musculature between the vessels and the thick adventitia of the veins.

FIG. 6.

Uterus and adnexa in the female pelvis. On left side tube extended. On right side tube bent and infundibulum in contact with ovary.

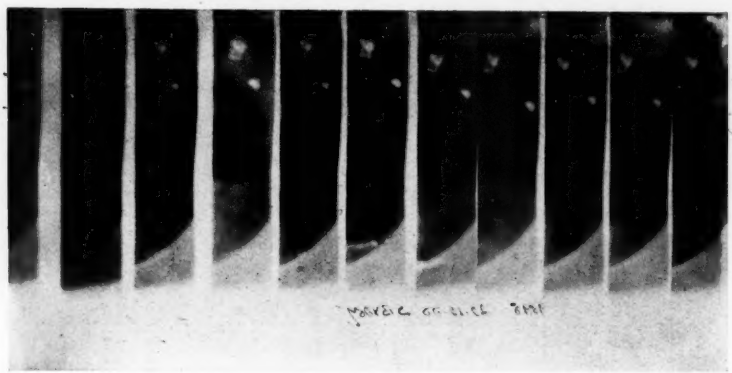

FIG. 7.

Case. 1. On serial film indicators in upper ovarian pole are seen to describe an up-and-down wave-like motion.

FIG. 8.

Case 2. In the ovary 4 lipiodol drops. The 2 small ones uppermost are the drop deposited in the upper pole split into two. They are separated from the two lower ones deposited in the free margin and lower pole. Above and medially a number of minute lipiodol drops lying free in abdominal cavity.

FIG. 9.

Case 2. Exposure 8 minutes after picture in Fig. 8. Ovary rotated so that upper drops are covered by that in margo libra.

FIG. 10.

Case 3. 20 minutes after onset of examination. In upper pole of ovary 2 indicators, in the lower one 1. Above upper ovarian pole infundibulum tubae is seen filled with lipiodol. Ovarian indicators projected below linea terminalis.

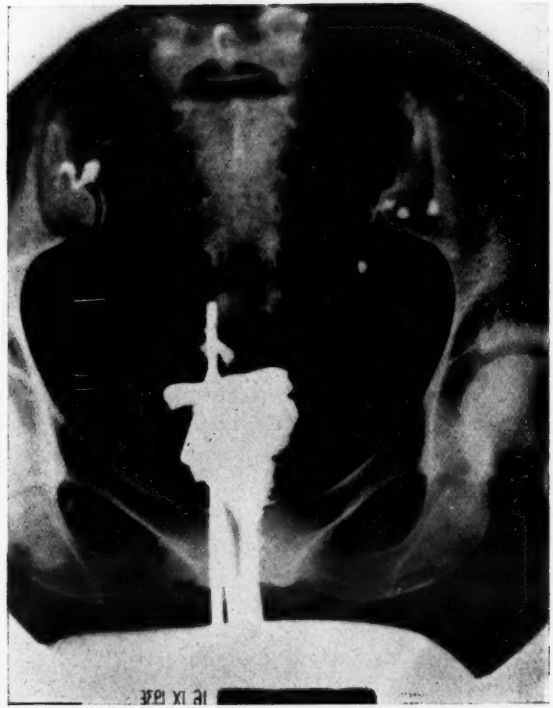

FIG. 11.

Case 3. 28 minutes after onset of examination. Upper ovarian pole projected above linea terminalis. Infundibulum lying at upper pole.

filled with lipiodol. Ovarian indicators projected below linea terminalis.

FIG. 12.

Case 3. 32 minutes after onset of examination. Ovary markedly displaced upwards and laterally.

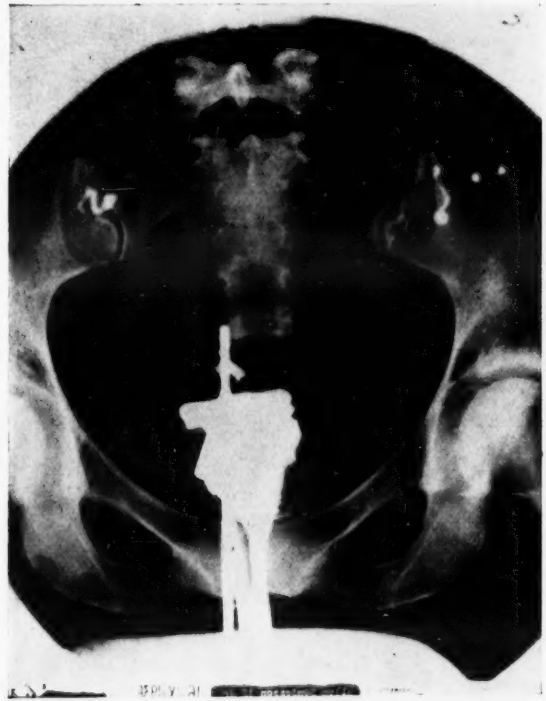

FIG. 13.

Case 3. 36 minutes after onset of examination. Ovary displaced still further upwards and laterally. Lower pole now above linea terminalis. Infundibulum lying at lower ovarian pole.

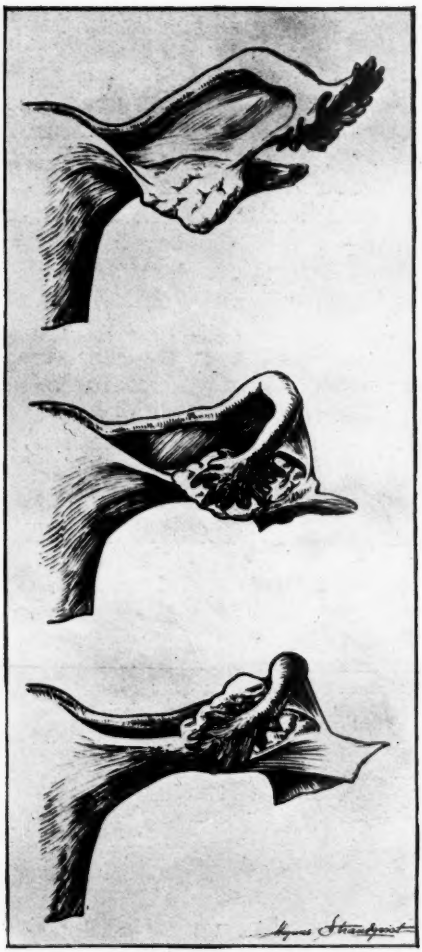

FIG. 14.

Diagrammatic representation of movements of tube and ovary. In upper picture tube extended. No contraction of musculature of ligaments. In middle picture a contraction is seen to have started. The tube has curved round the upper pole of ovary and fimbriae are in contact with this pole and one side of the ovary. In lower picture contraction stronger. Fimbriae reach lower ovarian pole and ovary is rotated so as to cause its other side to face the ostium abdominale tubae.

The intimate anatomical contact between tube and ovary during ovulation must, as has been pointed out above, tend greatly to safeguard the transit of the ovum to the tube after its liberation from the follicle. It is one of the many protective mechanisms utilized by Nature for safeguarding reproduction. However, experience shows, as evidenced by numerous observations of transperitoneal transit of ova and by cases of pregnancy in which the adnexa have been fixed through adhesions, that it is not necessary for this protective mechanism to function in order to enable the ova to be brought into the tube. The effect of suction and current towards the tubal ostium may undoubtedly be sufficiently powerful to enable the ova to be conveyed a relatively long distance through the general peritoneal cavity. That such is the case I was able to show experimentally in my earlier work on the physiology of the tube in rabbits, which work also included experiments in which the ostium abdominale and the ovary had been fixed at a definite distance from one another. But this investigation also made it clear that under such conditions the transit of the ovum to the tube by no means took place in such a reliable and sure manner as when the ingenious mechanism is set in function through which the tubal infundibulum on ovulation is placed in direct contact with the ovary.

Summary.

In two earlier works the author was able to show, definitely, that in rabbits as well as in monkeys (*Macacus rhesus*) the tubae uterinae no less than the ovary are capable of moving on their own accord, thanks to the smooth musculature embedded in the ligaments of the organs. This auto-mobility is of vital importance for facilitating the transit of the ovum from the ruptured follicle to the tube.

On ovulation the infundibulum is thus brought up and down across the ovary which itself turns to and fro on a longitudinal axis causing now one, now another of its surfaces to face the ostium abdominale. The fimbriae are distended and spread out over the ovary. From this we are able to conclude that the ovum never enters either an ovarian bursa or the general peritoneal cavity, but is directly transferred to the Fallopian tube.

In the present work these conditions have been studied in man.

The ligaments of the human adnexa contain a great amount of smooth musculature. In the lig. suspensorium ovarii numerous

muscle fibres have been shown to run parallel with the vessels. The adventitia of the veins is rich in longitudinal musculature.

In order to elucidate the function of the musculature small drops of lipiodol were injected at laparotomies beneath the tunica albuginea of the ovary. By these indicators one was able to study the position of the ovaries in the pelvis during subsequent radiographical examinations. When utero-salpingography was simultaneously carried out one was able to verify the anatomical relation of ovary and tube.

The serial photographs taken have shown the ovaries to possess considerable mobility. On account of varying states of contraction of the ligamentous musculature they are able to move cranially and caudally as well as laterally and medially. It was further shown that rotation of the ovary may take place on an axis parallel with its longitudinal axis. Finally it was shown that the tube could curve round the ovary in a bow-shaped manner.

On account of this mobility on the part of tube and ovary the infundibulum on ovulation can be placed in direct contact with the ovary which through rotary movements has the power of turning its various surfaces towards the ostium abdominale tubae.

In such circumstances the ova liberated from the ovary undoubtedly will never enter the general abdominal cavity but will be directly transferred from the ruptured follicle to the Fallopian tube.

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Menstrual Periodicity;

Statistical Observations on a Large Sample of Normal Cases.

BY

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I. INTRODUCTION.

THIS investigation was undertaken to obtain a series of accurate menstrual records from a large number of normal women. In 1927, when we first became interested in the periodicity of menstruation, we were able to find only one paper containing satisfactory scientific evidence on the subject, namely an account of a series of 56 cases by Foster.[1]

At that time, one of us was interested in reproductive rhythms bearing a definite relation to the phases of the moon, such as are found in certain invertebrates, and another of us in medical aspects of the subject. Since then, additional interest has been given to our investigations by the recent work on sex hormones and by the writings of certain other authors. One of these is Jolly's[2] theory of the duration of pregnancy in terms of suppressed menstrual periods; another is the theory of Knaus[3] on periodic fertility and sterility.

II. PREVIOUS WORK.

(*a*) *The Duration and Uniformity of the Interval Between Menstruations.*

Evidence on menstrual periodicity falls into two parts, depending on the method of obtaining data. The first section consists of histories, in which women describe to the observer their menstrual intervals of the preceding years. This is a large group, and it is almost valueless as scientific evidence. It is natural to estimate any interval exceeding 14 days in weeks or months, and it is, therefore, not surprising that the majority

of women, in answer to questions about their periods, say that the usual interval is 3 weeks, or 4 weeks, or a month (which may be variously recorded as 28, 30, or 31 days), or 5 weeks. This kind of evidence has led to statements to the effect that the commonest menstrual type is a 28-day one, but that a 30-day type occurs, and that 21-day and 35-day types are less common. An inquiry was conducted by a committee of the London Association of the Medical Women's Federation,[4] the data being obtained from over 6000 schoolgirls by the history-taking method. One of the findings of this committee was that the distribution of types was of the kind mentioned above, suggesting a predilection for whole weeks. The number of girls recording 21 days was considerably higher than the number recording 22 days, and similarly for 35 and 34 days. Other workers who used this method on young girls obtained similar results (Ski,[5] Tolentino,[6] Kosakaé and others,[7] Yang and Gear[8]).

Histories obtained from hospital or private patients of gynaecologists show the same preponderance of 21-day, 28-day, 30-day, and 35-day cases, with an implicit assumption of regularity. This is seen in the figures of Nakagawa[9] and Hajek[10]; but Sanes[11] writes: "In some of the 31-day type the menstrual flow appeared mostly on the same date (of the month) independent of the number of days in the month." This fact either points to mental influence on the date of onset of flow, or it casts doubt on the value of such records. Kennedy[12] also used hospital case records depending on histories. The best contribution to this class of evidence was made by Geist.[13] He collected histories from 200 hospital patients not suffering from pelvic disease, "obtaining with the greatest detail the exact days of each menstrual period for the entire year". He concluded that in most individuals there were deviations from the expected date varying from 5 days early to 10 days late.

In view of the large amount of evidence of the kind exemplified above, it is not surprising that the idea that menstrual periodicity is a matter of exact multiples of 7 days is stated or implied in many textbooks (Young,[14] Whitehouse,[15] Johnstone[16]). Novak[17] stated that in 80 per cent of normal women the interval between periods is 28 days, and that in the remaining 20 per cent it is commonly some multiple of 7 days. More recently, the same author[17a] (1933) omitted the "multiple of seven", but referred to the 21-day type, and the less frequent cases of intervals of 25 or 26 days, 35 days, and so on. Some of the textbook writers imply that there has not been any reliable

evidence on variations in menstrual periodicity by stating baldly that the cycle lasts about four weeks (Blair-Bell,[18] Berkeley,[19] Lovatt Evans[20]).

The other section of the evidence is derived partly from women who made a note of the beginning of each period in a diary or on a calendar, and partly from observers who interviewed the patients frequently or received communications from them regularly. The published evidence of this kind is rather meagre. It embraces 56 cases recorded by Foster,[1] 54 by King,[21a] 131 by Allen,[22] 76 by Fluhmann,[23] 100 by Engle and Shelesnyak,[24] 51 by Scipiades,[25] and 4 cases recorded by Richards,[26] a total of 472 cases. Even the diary method of obtaining data may be inaccurate, because the subject may neglect to note the date at the time, and may then fill it in wrongly some time later, either from an imperfect memory or on the assumption of regularity. Indeed, we have evidence that this method is not so reliable as one in which any delay in recording is plain to the observer. We did not depend on diaries in our investigation; and we include in our primary analysis only those women who recorded each menstrual period within a few days of its occurrence.

Foster's publication in 1889 appears to have been ignored until recent years. In his 56 cases the women kept records for 15 to 18 months, and only one of them had a regular cycle. She had a 26-day interval. All the others varied, and Foster was astonished at the amount of irregularity. When he read his paper, his medical brethren were sceptical and suggested that his subjects were abnormal. King's subjects were machinists, clerks, and college students; she concluded that in normal women the menstrual period did not occur regularly. Fluhmann found a marked variation in the menstrual cycle. He divided his 76 cases into two main groups. The first included 28 women who showed a certain degree of regularity, and the second group included the remaining 48 women, who showed marked irregularity. Scipiades, who was principally concerned with other aspects of the matter, came to the conclusion that variation in the intervals of one individual is the rule rather than the exception.

The work of Allen is one of the most satisfactory so far published. He obtained his data from nurses in training, who handed to the school nurse a note containing the menstrual data at the onset of each period. He found that although 87 women out of 131 cases thought they menstruated absolutely regu-

larly, they were, in fact, markedly irregular. This observation is of the greatest importance in interpreting data obtained from case histories. Actually, not one of these women was quite regular, and 30 of them were very irregular. He did not find noticeably large numbers of 21-day and 35-day cases.

Engle and Shelesnyak used statistical methods in the analysis of the menstrual data of 100 adolescent girls in a Jewish orphanage in New York. They found, among other things, that irregularity of the cycle was the rule, and that the variability decreased with increasing menstrual experience.

Finally, Holt,[27] in a critical review based partly upon his own unpublished data, writes of the woman whose periods recur regularly as a *Märchenprinzessin*—a princess out of a fairy story.

It is thus clear that the results of investigations on menstrual periodicity published during the last decade or so vary very widely and in contradictory fashion. The few accurate records suggest that the current view of the regularity of menstruation is erroneous. Our results should assist in resolving some of the contradictions.

(*b*) *Lunar Periodicity in Menstruation.*

Menstruation recurs about once a month (*mensis*, month), and the moon goes through a cycle of changes in about the same time. The lunar cycle was much more important in the lives of the ancients than it is to us, and it is not surprising that the coincidence in the periods of the two cycles should have been noticed. The belief that there is some causal relation between the two is thus quite old (Fox[28a]). Many people nowadays are inclined to ridicule this belief. In animals other than man, however, there are many cases in which behaviour—and particularly sexual behaviour—is undoubtedly connected with the moon's phases. Most of these are apparently caused either by the additional light of the full moon, as in certain nocturnal insects (Hora,[29] Williams[30]), and others by the cycle of spring and neap tides, as in the marine worm, *Nereis* (*Platynereis*) *dumerilii* (Hemplemann[31]). There remain, however, a few cases in which a satisfactory explanation has not been found for a distinct lunar rhythm in spawning. One such case is that of the sea-urchin, *Centrechinus setosus*, at Suez (Fox[28*]), in which spawning is at a maximum at full moon and at a minimum at new moon; another case is provided by the scallop or quin, *Pecten* (*Chlamys*) *opercularis*, near Plymouth (Amirtha-

* This paper includes a review of both classical and recent references.

lingam[32]). The quins examined were taken from the bottom of the sea in about 40 metres of water, where practically light does not penetrate. The difference in range between new moon spring tides, when less spawning occurred, and full moon springs, when spawning was at a maximum, was only about 0.6 metres.

When it is borne in mind that these lunar rhythms in reproduction do exist and are due to unknown causes, it is easier to accept the possibility that there is a lunar rhythm in menstruation, perhaps due to similar causes. Indeed, Arrhenius[33] concluded from details of about 12,000 menstruations that there is such a rhythm. His work is discussed below in connexion with our results. As recently as 1933, De Lee[34] stated that the majority of women menstruate during the new moon, while Fluhmann took the view that "traditional beliefs and lunar superstitions" have had too strong a hold on the medical profession. Arrhenius's conclusions have never been tested, and it seems worth while to try either to place them in the category of reliable knowledge or to refute them once and for all.

III. The Data.

(*a*) *The Collection of the Data.*

In attempting to assess some character of the population as a whole, it is important that the sample of the population studied should be as nearly representative or random as possible. Accordingly our data are not derived from patients in hospitals or attending clinics, but from volunteers. The method of obtaining the volunteers was to send to people we knew a printed letter, inviting them to help by sending us their own menstrual data and by giving us the names and addresses of others who might do the same. In addition to this individual method, organizations were approached. Unfortunately, employers of labour were not helpful, with the result that our sample is almost entirely derived from the professional classes.

Apart from this, there is a further element of selection in that the records were obtained from volunteers. The personal considerations which would influence a woman in consenting to send records are impossible to assess. The authors are not agreed upon the question of whether the voluntary method of recording would tend to bias the results in favour of or against normality. We consider, however, that the sample does not deviate widely from a truly random sample in this respect.

About 950 women consented to send in *data*. An index number was allotted to each of these, so that her name was never asso-

ciated with her data. A key list was kept in one place (Birmingham) and the data in another (London), and correspondence was sealed and forwarded under the number to the holder of the key, who then addressed it. The data themselves were eventually renumbered, so that secrecy was completely assured.

The investigation was planned so as to obtain one year's data from each individual. To each were sent a *questionnaire* and some stamped, addressed, and numbered record cards. Each person was asked to post a record card immediately after the beginning of each menstruation, giving the time and date of the onset of flow and an indication of the severity of the symptoms. Further cards were sent out as required. At the end of the year a second *questionnaire* was circulated. The *questionnaires* obtained information about the age and occupation of the women, the symptoms associated with the menstrual cycle, the age at the *menarche*, and a number of other items which are not dealt with in this publication. The second *questionnaire* asked, among other things, for details of any particularly long intervals during the preceding year. Thus, if there was a long interval in a postcard record which was not reported in the second *questionnaire*, there was reason to believe that a record rather than a menstruation had been missed, and the case was classified accordingly (see below).

(*b*) *The Classification and General Treatment of the Data.*

In due course, the data from the record cards were tabulated, together with the post-marked date of posting, so that some estimate of the promptness of posting, and thus of the reliability of the data could be made. The time intervals between the onsets of successive menstruations and the average of these intervals were worked out for each case, and then the cases were classified.

The classification was based upon (*a*) the extent of the information sent, e.g. the number of *questionnaires* filled in, and (*b*) the apparent reliability of the data. Thus Class I contained women who returned both *questionnaires* and at least one year's records; Class II defaulted only with the second *questionnaire*. Grade A contained records with no apparent discrepancies between postcards and *questionnaires*, and with not more than two cards posted more than 10 days after the onset of the period recorded. Grade B included cases in which there was one discrepancy of a not very serious kind, or in which there was a slightly greater degree of delay in posting than was per-

mitted for Grade A. Such cases are satisfactory for working out average intervals, provided there is no doubt about the first and last dates of the series or about the number of intervals. Such comparisons as could be made showed that this process of classification did not reduce the random character of the data selected for the fullest treatment—namely Group 1A.

In all, 852 people sent information of some kind. Of these, 209 were classified as 1A, apparently quite reliable, while a further 561 returned at least the first *questionnaire* and sufficient date records to provide some evidence about periodicity.

IV. Distribution of Average Intervals Between Menstruations.

The classification of women into "menstrual types" is a conspicuous feature of the literature which we have reviewed. The unjustifiable character of such classifications is clearly seen from Table I and Fig. 1, which show the frequency of each average interval. It will be seen that not one of the women in the top four groups had an average interval below 22 days; if, however, averages of 22, 23, and 24 days are counted as 3 weeks, as we believe many previous workers have counted them, then about 7 per cent of all the cases fall into this class, a proportion not differing greatly from those mentioned in the literature.

The top four groups gave consistent results. Only about 2 per cent of women had an average interval of less than 24 days, and 3 per cent of 37 days or more; 97 per cent had averages of 24 to 36 days, and 78 per cent of 25 days to 31 days.

An ideal classification should be as natural as possible. There should either be no cases intermediate between classes, or, if that is not possible, the number of intermediates should be small compared with the number of cases undoubtedly falling inside the class limits. These requirements are by no means satisfied by the usual classification. An examination of Fig. 1 shows that a natural classification is impossible. The commonest average intervals are 26, 27, and 28 days. Women with average intervals longer than 28 days become progressively fewer as the difference between them and the 26 to 28-day group increases. Thus there are in Group 1A 21 women with an average of 29 days, 19 with 30 days, 14 with 31 days, 8 with 32 days, and so on. Similarly, the numbers become progressively fewer for the shorter interval cases. The only possible classification seems to be that implicit in the figure, namely to describe

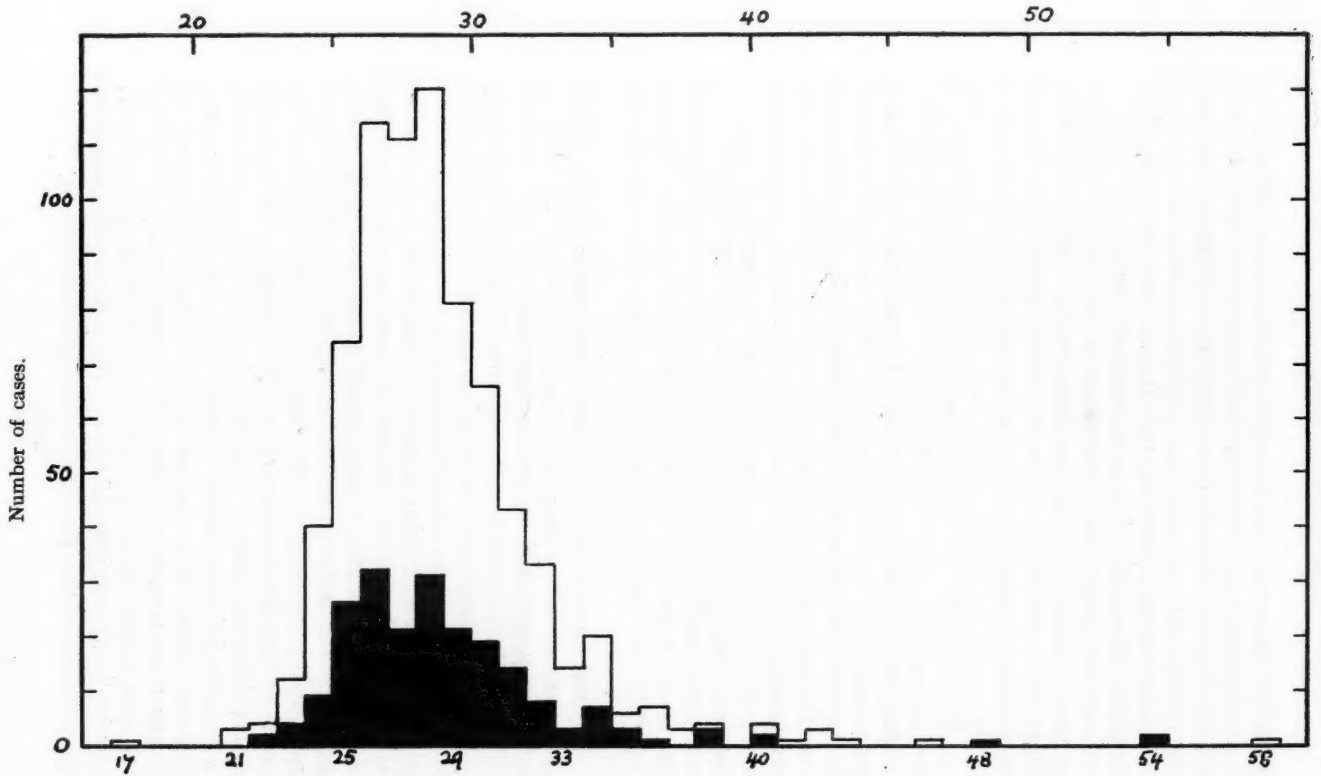

FIG. 1. Average interval between the onsets of successive menstruations. The solid figure represents the 209 cases of Group 1A, and the outline figure all 770 cases. Intervals of, say, 28 days up to but not including 29 days, are plotted as 28-day intervals. Compare Table I.

TABLE I.

Average interval days	Number of cases: Group 1A	Groups 1B, 2A, 2B	Other groups	Groups 1A, 1B, 2A, 2B	All
17	—	—	1	—	1
21	—	—	3	—	3
22	2	1	1	3	4
23	4	3	5	7	12
24	9	16	15	25	40
25	26	22	26	48	74
26	32	43	39	75	114
27	21	41	49	62	111
28	31	36	53	67	120
29	21	29	31	50	81
30	19	22	25	41	66
31	14	17	12	31	43
32	8	15	10	23	33
33	3	4	7	7	14
34	7	8	5	15	20
35	3	2	1	5	6
36	1	4	2	5	7
37	—	1	2	1	3
38	3	1	—	4	4
40	2	2	—	4	4
41	—	1	—	1	1
42	—	1	2	1	3
43	—	—	1	—	1
46	—	—	1	—	1
48	1	—	—	1	1
54	2	—	—	2	2
58	—	1	—	1	1
Totals ...	209	270	291	479	770
Average case	29.0 days	28.9 days	28.3 days	29.0	28.7
* Standard deviation	±4.31 days	±3.71	±3.27	±4.09	±3.74
* Standard error	±0.30 days	±0.23	±0.19	±0.19	±0.13

For each individual, the average interval between the onsets of successive menstruations during the year was worked out. The table shows the frequencies of these average intervals.

* See Statistical Appendix I.

and the outline figure all 770 cases. Intervals of, say, 28 days up to but not including 29 days, are plotted as 28-day intervals. Compare Table I.

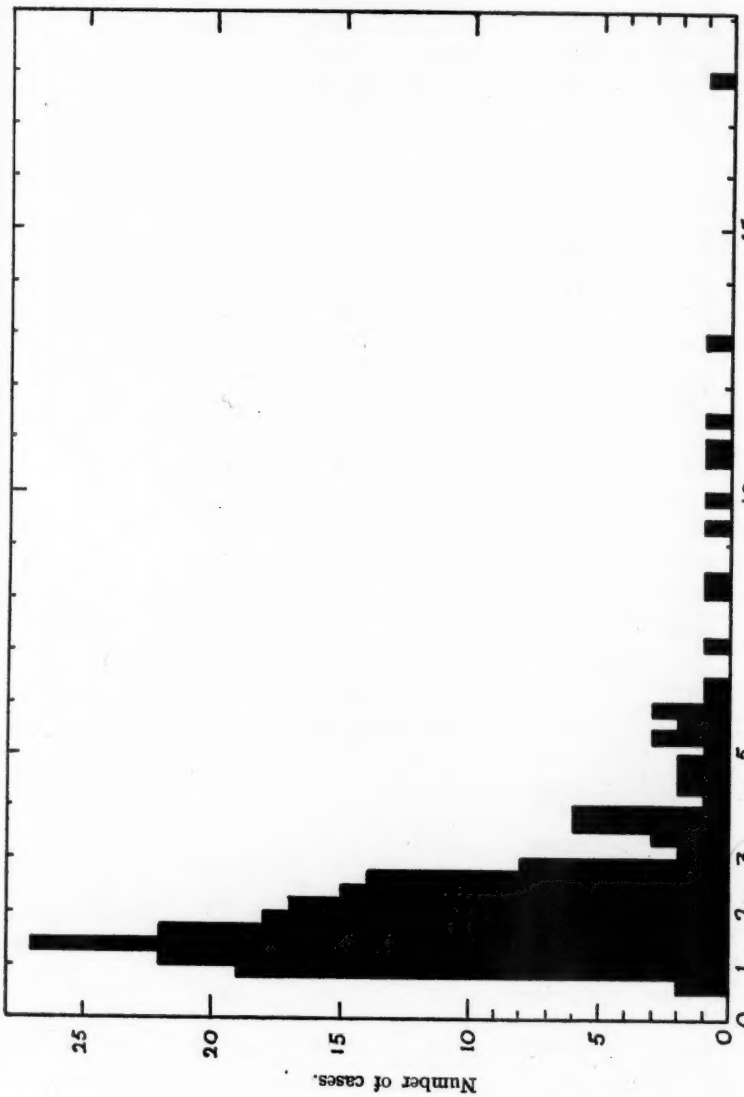

FIG. 2. Irregularity of the menstrual cycle. From the 209 cases of Group IA.

the case of woman whose average is from 22 days inclusive up to but not including 23 days as a 22-day case. The classes so created satisfy the requirement of being mutually exclusive, though they are not natural classes. It still remains a question whether or not such a classification is of value, for if a given individual belongs to the 22-day class in one year and the 33-day class in the next, it would seem useless to classify individuals at all. This question is dealt with later under the heading of variability.

If the average interval of each case is treated as one observation, then the average of the 209 observations in Table I is 29.0 days. Regarding this figure as the average duration of the menstrual cycle, we see that it differs from the average interval of the largest classes of cases, which are 26 days, 27 days, and 28 days (i.e. from 26 days inclusive up to but not including 29 days). This is reflected in the asymmetrical form of Fig. 1, where there are scattered cases in which the women had high averages up to 54 days, but no satisfactory cases at all having low averages below 22 days. It is impossible to have cases as much shorter than the average as 54 days is longer than the average; presumably, also, there is a minimal time required for the structural and physiological changes of the reproductive cycle, but a maximal time is not so sharply marked. It is not known whether these women with very long intervals have a period corresponding to the anoestrous period of some other mammals.

V. Variability in the Individual.

It has been said that "the only regular thing about the regular monthly period is its lack of regularity." ("An der Regel ist das einzig Regelmässige die Unregelmässigkeit"—Fraenkel[35]). What does "regular" mean? As soon as we examine this question, we see that "absolutely regular" can only mean something rivalling a master-clock at Greenwich. What we can concern ourselves with, however, is the *degree* of irregularity.

Table II gives a list of the successive intervals, in order of occurrence, of selected cases from Group 1A. Case No. 2875 is the most regular one we have. The intervals of this woman vary from 25 days 19 hours to 28 days 13 hours, a range of nearly 3 days. So far as our evidence goes, then, there are no women with variations of less than ±1 day. The very regular case is either an absolute myth, or it is so rare as to be a medical curiosity.

TABLE II.

Duration of successive intervals in order in cases selected from Group 1a.

Case No. 2875		Case No. 2159		Case No. 2059	Case No. 2048	Case No. 2036	Case No. 2041	Case No. 2040	Case No. 2054
Days	Hrs.	Days	Hrs.	Days	Days	Days	Days	Days	Days
27	6	23	0	25	26	30	30	26	42
28	12	22	14	25	24	35	36	26	58
27	16	22	23	26	27	32	26	27	87
28	4	23	12	29	29	37	32	20	54
28	12	23	22	25	26	34	39	25	48
27	17	22	8	24	29	29	34	26	56
27	5	22	8	24	28	35	16	24	36
28	13	23	20	25	26	35	36	25	—
25	19	19	20	29	23	28	31	25	—
26	7	24	12	24	29	29	28	39	—
27	16	25	19	23	27	30	32	36	—
27	21	22	17	22	27	27	29	31	—
28	13	25	17	27	23	32	30	39	—
27	14	23	19	24	22	27	—	26	—
—	—	24	5	27	25	—	—	—	—
—	—	24	14	25	23	—	—	—	—
—	—	23	8	—	—	—	—	—	—
				Average interval:					
27	16	23	11	25.2	25.9	31.4	30.7	28.2	54
				* Mean deviation:					
±0.6 days		±1.0 days		±1.5	±1.9	±2.9	±3.9	±4.6	±11

In the light of this conclusion an examination of the data on which Table I and Fig. 1 are based indicated that many of the averages of the 291 cases in "Other Groups" are of little value. Thus the woman in the solitary 17-day case returned only two record cards. If the woman of case No. 2159 (Table II) had also recorded only one interval and that one the ninth on our list, she would have been entered as a 19-day case, instead of a 23-day one. That is to say, averages based on a small number of intervals are unreliable, owing to the variability, and for that reason we do not attach much importance to our inferior groups. Their results are set out here, however, to show that they do not differ greatly from the more reliable

* See Statistical Appendix I.

groups; this tests our classification and shows that it has not biased our conclusions.

It must be accepted, then, that there is a considerable variability in the interval between the onsets of successive menstruations in each individual. A convenient measure of variation in an individual is the mean deviation from the average per period.* This has been worked out for Group IA, and the results are shown in Fig. 2. This figure shows that only two women had mean deviations of less than ±0.74 days, and both of these varied by more than ±0.50 days per interval. The women in the largest class of cases, 27 in number, varied by ±1.25 to ±1.49 days per interval, and the average mean deviation for the whole group was ±2.59 days. What these figures mean in terms of a single series of intervals can be seen in Table II, in which the examples have been chosen for this purpose. Most of the very variable cases, though not all of them, had high average intervals. The central value was about ±2 days, so that about half the cases had a mean deviation lying between 0.5 and 2 days, and half a higher one. Altogether 78 per cent of the 209 cases had a mean deviation below ±3 days, and 87 per cent below ±4 days. Mean deviations greater than ±4 days occurred in the remaining 13 per cent of the total, and in 5 per cent (10 cases) the mean deviation was greater than a week.

Between the ages of 20 and 40 the mean deviation was found not to vary much.

The 19 married women in Group IA gave an average value of ±1.88 days to ±0.28. In comparing this with the average for spinsters, allowance was made for the correlation of mean deviation with average interval in the long interval cases, and an expected average was calculated for spinsters of the same average intervals ±2.40 days. The difference in variability was thus not significant, though it might easily prove to be so with a larger number of married women.

A more vivid picture of the variability of the interval is perhaps provided by the difference in length between the shortest interval and the longest one (D.S.L.). Only 9 per cent of the 209 Group IA cases had a D.S.L. of less than 5 days, and 16 per cent of less than 6 days, while 30 per cent (62 women) had a D.S.L. of 13 days or over. In all the 12 women with a mean deviation of ±6 days or over, the D.S.L. was over 30 days. One of these had an average interval of 25 days, 1 of 31 days, 3 of 32 days, and the rest longer ones. Of the 45 women

* See Statistical Appendix I.

(22 per cent) having a mean deviation of ±3 days or over, only two had a D.S.L. under 13 days. The average D.S.L. for all 209 cases was 12.6 days and the central value was 9 days.

Considering only the 78 per cent of cases in which the mean deviation was less than ±3 days, the average D.S.L. was 8.4 days and the central value was 8 days. We may, rather loosely, regard these cases as the normal ones (Fig. 2) and then we must regard the variation of between 8 and 9 days as representative of normal people. This has some importance in connexion with Knaus's[3] theory (see pp. 862–3).

The next feature to look for is some characteristic of individuals by which we can typify them. Even though the intervals are not uniform in length, the yearly averages may be so. In Table II the woman in Case No. 2040 usually had intervals of about 25 or 26 days, but she had a run of 4 intervals between 31 and 39 days long; but a close examination of the data on which the table is based shows that this is strikingly exceptional. In most cases the intervals cluster round the average (Fig. 3). Thus in the woman in Case No. 2159 the intervals are of 22–25 days, with 1 exception of 19 days, and in that of Case No. 2036, they vary from 27 to 37 days. It looks as if the difference between these two women, as expressed by their respective averages, is a real one (see Statistical Appendix II). If such a difference were maintained from year to year, then we might adopt the common view, namely that certain individuals do on the whole have shorter intervals than certain others, and we might perhaps speak of 24-day cases and so on.

Table III summarizes the evidence on this question. A certain number of women responded to a *questionnaire* request to send in past records from their diaries. From these dates, extending over 8 and 16 years, the intervals were worked out, and then the average interval for each year. These data are subject to the sources of error previously mentioned (p. 841), but since only the average interval is required they will serve for this purpose (see p. 844).

In 16 cases, Nos. 2183, 2500, and 2908, the maximal difference between a single year's average, and the grand average is 0.75 days. Thus the woman in Case No. 2183 varied from 27.7 days to 29.0 days. That is to say, in one year she was a 27-day case, and in another a 29-day one, but she certainly does not look like becoming a 24-day or a 34-day case. It is, therefore, not correct to speak of an individual as a 28-day case, because she is likely to fall into a different category

TABLE III.

Successive yearly average intervals in certain cases, from diary records.

	Case No. 2183	Case No. 2500	Case No. 2627	Case No. 2810	Case No. 2908
Average intervals for successive years	27.7	25.8	25.6	29.3	26.7
	28.2	26.0	25.1	28.3	26.1
	28.5	26.2	25.5	29.8	27.1
	28.2	24.9	26.4	28.3	26.6
	28.7	24.9	25.2	28.1	—
	29.0	26.0	25.0	27.3	27.3
	28.2	25.6	25.7	28.2	26.9
	28.4	24.2	24.1	27.6	27.0
	28.4	—	24.3	27.2	26.6
	—	—	—	27.3	27.1
	—	—	—	26.1	26.4
	—	—	—	26.2	—
	—	—	—	26.9	—
	—	—	—	26.6	—
	—	—	—	25.7	—
	—	—	—	26.2	—
Grand average ...	28.4	25.45	25.2	27.4	26.8

in the following year. She may properly be termed a 27-29-day case. This term must on no account be supposed to imply that all the intervals are 27 to 29 days long, but that the intervals cluster round these figures as the yearly averages, just as the individual heights in a population cluster round the average (Fig. 3).

Case No. 2627 is not fundamentally different from the three cases just mentioned, but Case No. 2810 shows a difference from the others which is dealt with later, under the heading of average interval in relation to age.

These data (Table III) are unfortunately not suitable for a test of constancy of variability in each individual, since we have no check on the accuracy of recording of the separate intervals.

VI. SOME POSSIBLE CAUSES OF VARIATION.

(*a*) *General.*

It has been pointed out above that the frequency curve of intervals of various lengths (Fig. 3) is similar to many curves which show the frequency distribution of sizes of a measured

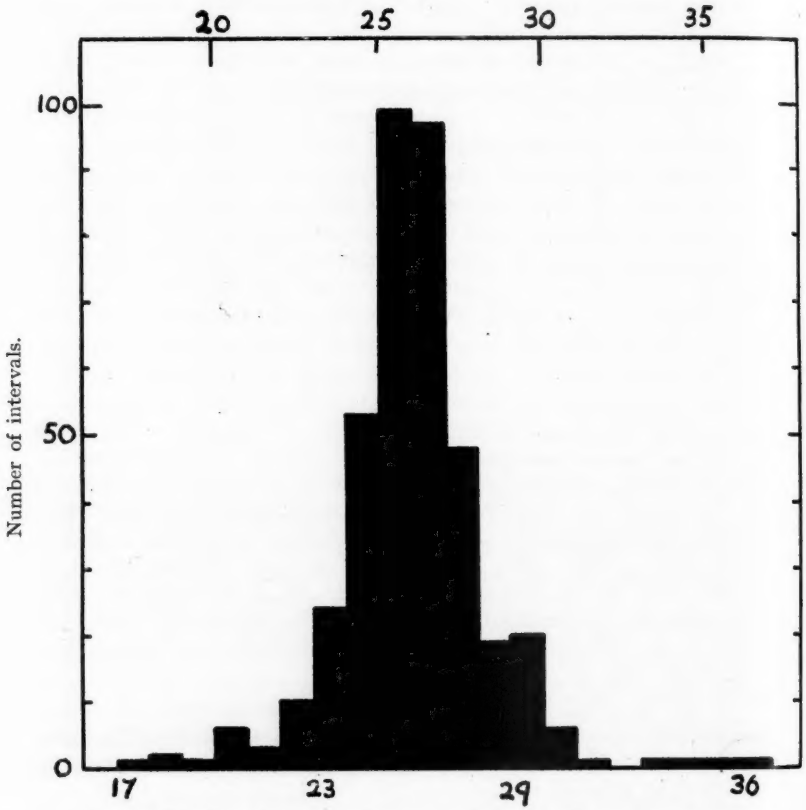

FIG. 3. Distribution of separate intervals in twenty-four Group IA cases whose average interval was 25– days, including 394 intervals in all.

characteristic in a population, and in fact this curve approximates to the so-called normal distribution. This is the kind of curve which is obtained when many factors, none of which is predominant, tend to alter the character from its essential size. It is not unreasonable to suppose, therefore, that there is a certain essential length of menstrual cycle in the human race. The average length differs in different individuals (Fig. 1); this is perhaps due partly to the influence of a large number of genetical factors, which alone would produce a normal distribution even in a uniform environment, and partly to environmental factors. In the same way, the variation of the separate intervals in an individual may be attributed to the influence of a large number of environmental factors. This section, VI*b*, will be devoted to the question of whether or not the duration of one interval influences the duration of its successor. The following sections will test for (VII) correlations of average intervals with occupation, age, and season of the year, and (VIII) correlations of the date of each occurrence with certain external cycles, namely the days of the week and the lunar cycles.

(*b*) *Correlation of One Interval with its Predecessor.*

Correlation of a particular interval with its neighbours might be either positive or negative. If positive, the tendency would be for long intervals to occur in runs, each followed by a run of short intervals; if negative, it would mean that each short interval tended to be followed by a long one, and *vice versa*, so that there would be a quick return to the general average. A careful examination of Table II shows that both of these phenomena occur. Thus the woman in the very exceptional case, No. 2040, there are 9 successive intervals of 20–27 days, followed by a run of 4 of over 30 days. Here the intervals are positively correlated with their neighbours. Case No. 2048 shows the same kind of correlation, though a much smaller one. Iu Case No. 2041, on the other hand, an interval longer than the average tends to be followed by one shorter than the average. This case shows a negative correlation of successive intervals, though only a small one.

Mere inspection of the data does not tell us if these correlations are general or accidental. A statistical analysis is necessary. The analysis used on the first 30 cases in Group IA is summarized in Statistical Appendix IV. It gives a correlation of -0.012 days, and a significance so low that we can be sure that there is no resultant correlation worth bothering about. In short, the length

of each interval is independent of the length of its predecessor, so that we can legitimately use the methods outlined in Statistical Appendix III.

VII. Average Interval in Relation to Certain Possible Factors.

(*a*) *Occupation.*

The information available under this heading is summarized in Table IV. The occupation of each subject was taken from the first *questionnaire*. The average given in the table is found by dividing the sum of the individual averages in each group by the number of women in the group. Thus the sum of all 770 averages was 22,106.9, which gives the general average of 28.7 days when divided by 770. Incidentally the table is useful in another way, in that it shows how far we have succeeded in getting a random sample of the population, in respect of occupation.

Table IV.

Average interval in relation to occupation.

Occupation	Group 1A		Groups 1B, 2A, 2B		Other Groups		All	
	No.	Av.	No.	Av.	No.	Av.	No.	Av.
Student (physical training) ...	13	32.1	17	29.7	31	29.6	61	30.1
Student (mostly science or medical)	41	30.1	63	29.6	53	29.0	157	29.6
University lecturer, research, etc.	14	29.7	18	28.5	10	27.2	42	28.6
Teacher (physical training)	47	28.2	41	29.8	45	27.7	133	28.5
Teacher (general)	32	29.2	46	28.2	39	28.1	117	28.5
Housework	19	28.8	23	28.7	27	27.8	69	28.4
Clerk, typist, secretary, etc	11	27.8	15	29.0	11	28.1	37	28.4
Nurse	11	27.1	15	28.2	34	28.7	60	28.3
Others	21	27.6	32	27.4	41	27.9	94	27.6
Total averages	209	29.0	270	28.9	291	28.3	770	28.7

In Table IV consider first the end column headed "All." Apart from the two student categories and the "Others", the average by occupation varies only between 28.3 and 28.6 days. A careful examination of the constituent groups of the six uniform categories does not reveal any large or consistent occu-

pational effect. It must be borne in mind that a dozen cases are not enough to make a small difference of average important. On the other hand, the differences shown by the students and "Others" are consistent.

In no category except the "Others" is the average below 28 days in all 4 columns. Similarly, only in the 2 student categories is the average higher than 29 days in all 4 columns. Now, one of the obvious differences between students and teachers is that students are younger. Again, the "Others" category contains 37 women trained in physical education, many of whom were not teaching but holding superior posts in the subject, 4 matrons, 16 medical practitioners, and others of more mature age. These facts suggest that there is a correlation between age and average interval, a suggestion which is tested in the next section of this paper and found to be correct.

Apart from the three categories in which the age correlation shows clearly, there is quite fair uniformity in average interval. That is not to say that there are not any occupational differences of average; but there are no such differences of the same order of magnitude as the age differences.

(*b*) *Age.*

The data on average interval in relation to age are summarized in Table V. In Group IA the age of one woman was uncertain, so she was omitted; otherwise the material is the same as for Tables I and IV.

TABLE V.

Average interval in relation to age.
The average intervals are for the period Nov. 1928 to Aug. 1930.

Year of birth	IA			IB, 2A, 2B			IA, IB, 2A, 2B		
	No. of cases	Av. days	S.E.*	No. of cases	Av. days	S.E.*	No. of cases	Av. days	S.E.*
1877–1890 ...	24	27.0	±0.52	25	26.8	±0.42	49	26.9	±0.34
1891–1895 ...	25	27.4	±0.48	28	27.3	±0.37	53	27.4	±0.26
1896–1900 ...	34	27.6	±0.47	48	29.0	±0.47	82	28.4	±0.35
1901–1905 ...	63	29.9	±0.72	89	28.8	±0.39	152	29.2	±0.57
1906–1910 ...	59	30.1	±0.50	77	30.1	±0.51	136	30.1	±0.36
1911–1915 ...	3	32.1	±2.1	3	30.8	±0.63	6	31.5	±1.3
Totals	208	29.0	±0.30	270	28.9	±0.23	478	28.9	±0.19

* See Statistical Appendix I.

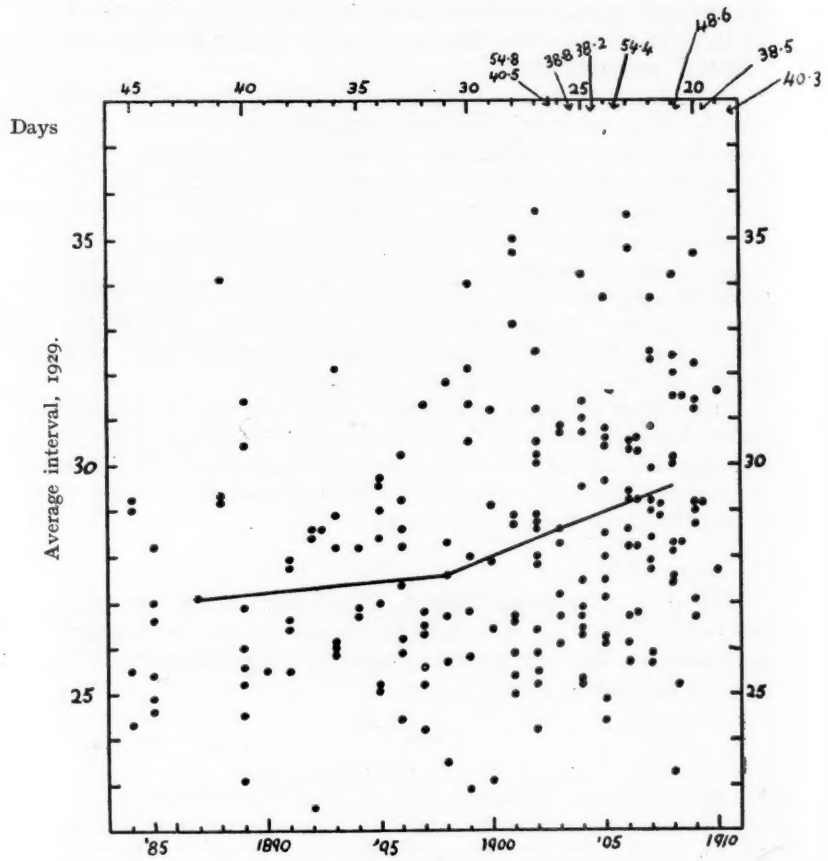

FIG. 4. Average interval and age. In order to allow a large-scale figure, averages of 38– days and over are entered as numbers, and females born before 1884 (1) and after 1910 (3) are omitted. The line joins the five-year averages of the *points*, except that the females born from 1884 to 1890 are put into one class to give a seven-year average because these cases are few. Thus the long interval cases are omitted from the averages, but even so there is an evident decline in average interval with increasing age.

In Group 1A there is a continuous fall in average interval with increase in age of subject (Fig. 4). In Groups 1B, 2A, 2B, the same is true except for the years 1896–1900. For these years the difference between Group 1A and the other groups is rather large (1.4 days), and is unlikely to happen by chance (3 chances in 100), so that it looks as if there is some important cause of variation other than age. Apart from that, the averages in the two columns agree remarkably well. It is, therefore, best to carry out the more detailed tests on all four groups combined (last column).

In no case is the difference between adjacent age-groups sufficient (compared with its standard error) to be important; but in every case, excepting the small group of the youngest women, the differences between alternate age-groups are large; the chances are at least 300 to 1 against their being accidental. Thus the difference for 1896–1900 and 1906–1910 is 1.7 days ±0.50, so that the betting is about 1,600 to 1 against the difference being accidental (see Statistical Appendices I and II). The fall in average with increasing age occurs in every age-group, which makes accidental occurrence even more unlikely.

The 47 married women also showed the age effect, though more erratically, presumably because they are few. Their removal from Table V had no material effect.

We may therefore say that the average interval in 1929 becomes less and less as we pass from the younger women to the older. Omitting the first and last groups for the sake of homogeneity, the fall in average has a mean value of 0.18 days per annum.

It is impossible for the whole of this fall to be due to the students, for it continues at ages when student life is long past. It seems proper, therefore, to explain the high average for students by their age, and not to explain the high average for young people in this sample by the fact that most of them are students.

We cannot infer, from these observations on a single sample, that the average interval of each individual falls with increasing age; nor does an examination of Table III lead to such a simple conclusion. Case No. 2810 (Table III) shows the fall clearly, but the others do not. In other less complete and extensive records some cases show a fall, others a rise, and still others no certain change at all. Though the general tendency seems to be towards a fall, these additional records are not good enough to justify a more sweeping generalization.

It is possible that the population as a whole has been changing its average interval, and that the individuals have not changed. Thus social habits, wars, and the like may have permanent effects on the periodicity of the young girl; or natural selection may be weeding out the short interval cases. It is also possible that our cases do not form a random sample for this purpose. We do not say these are probabilities, but they are possibilities which are not excluded by our data and which would fit them. The differences between age-groups are rather big for an evolutionary change, and we incline to the view that the average interval of the individual tends to get less with advancing years.

Any comparison of the average intervals of different groups of women should make allowance for an age effect. For this reason comparisons between our averages and those of other authors who do not give the age distribution in a suitable form are useless. A comparison within our own data indicates a suitable method. The average intervals of the age-groups of spinsters were worked out. The average interval for each age-group of spinsters was then multiplied by the number of married women in the same group, and the total for all age-groups of married women was divided by their number. This gave the expected average interval of the married women, if they do not differ from spinsters, 27.8 days. The actual average of the 47 married women in the 4 groups of Table V was 28.7 ±0.54 days. This difference of 0.9 days is less than twice the S.E. of the one average (±0.54), so that the married women were not significantly different from the spinsters in this respect (see Statistical Appendix II).

(*c*) *Season of the Year.*

In the 209 cases of Group IA, each interval was marked as longer or shorter than the average for the individual. Out of 3,024 intervals differing from the average, 1,631 (54 per cent) were shorter and 1,393 (46 per cent) were longer than the average. The divergence from the 50:50 ratio is due to the fact that longer intervals were often much longer than the average, while shorter ones were not often so much shorter (cf. Figs. 1 and 3). The intervals were then divided between the quarters of the year according to the date of the end of the interval. Starting with the winter quarter (January to March inclusive), the percentages of intervals shorter than the average were 54.6, 53.0, 54.3, and 54.2 respectively. There is thus no general tendency to a

cyclical change in the proportion of intervals longer than the average during the year. There may be cyclical changes of this sort in individuals, but if there are they work in one direction in some cases and in the opposite direction to an equivalent extent in others.

There is a good deal of recent work showing that the annual cycle of natural light intensity has controlling effect on the sexual cycle of some mammals and birds (Marshall).[36] Even if this influence was effective on primitive man, the above results show that it has no great effect on the interval between the menstruations of adult women under civilized conditions.

VIII. The Date of Menstruation in Relation to certain External Cycles.

(*a*) *Weekly Periodicity.*

An examination of the data was carried out to see if there was any general tendency for menstruation to start, say, at the week-ends, or on Wednesdays. The number of women (IA) starting to menstruate on each day from November 3rd, 1928, to August 31st, 1930, was first tabulated. The numbers thus obtained were then written down in order in horizontal rows of seven, so that the numbers for Sundays, for example, came in one vertical column. Each of the seven vertical columns was then added up, so that the number of onsets was known for each day of the week for the 22-month period. The data for the other groups were treated in the same way, and the results are summarized in Table VI.

Considering all the records together (last column, Table VI), the average number of onsets per day is 1,488. For every day the actual number of onsets differs from this average. The χ^2 test (Fisher[37]) guides us in deciding whether the differences from the average are fortuitous or not. For all the data together, the test gives a probability of 0.025 (25 chances in 1,000) that the divergences are accidental.

Careful examination of all the columns shows that nearly all the numbers below average occur during the first three days of the week, and most of the higher numbers on Thursdays, Fridays, and Saturdays. The first two columns are fairly consistent, and the inconsistencies of the third column of less reliable data are not sufficient to eliminate their effect on the total. Accordingly the data were grouped so as to show up the differences (Table VII).

TABLE VI.

Number of menstruations starting on each day of the week, from November 3rd, 1928, to August 31st, 1930.

Day	Group 1A	Group 1B, 2A, 2B	Others	All
Mondays	456	551	422	1429
Tuesdays	440	570	417	1427
Wednesdays ...	443	572	448	1463
Thursdays	508	612	472	1592
Fridays	483	582	414	1479
Saturdays	476	628	436	1540
Sundays	466	563	457	1486
Totals	3272	4078	3066	10,416
Average per day	467	583	438	1488
*χ^2	7.36	7.86	6.61	14.4
p	0.29	0.25	0.37	0.025
		χ^2 = 12.53		
		p = 0.05		

TABLE VII.

Distribution of onsets of menstruation over the parts of the week. Data from Table VI.

Days	Group 1A	Group 1B, 2A, 2B	Others	All
Mondays to Wednesdays	1339	1693	1287	4319
Thursdays to Saturdays	1467	1822	1322	4611
Sundays	466	563	457	1486
Totals	3272	4078	3066	10,416
χ^2	5.84	5.55	1.43	9.55
p	0.05	0.06	0.48	less than 0.01
		χ^2 = 10.97		
		p = less than 0.01		

* See Fisher[37] (1932).

In Table VII, the χ^2 test applied to the first two columns together, and to the whole of the data gives a probability of less than 0.01. This is sufficiently small (less than 1 in 100) for us to say that the divergences are probably not due to random errors. Sundays' values are substantially average, so that we can say that there is a slight but real tendency to start to menstruate on Thursday, Friday, or Saturday, rather than during the earlier part of the working week. The average proportion of onsets for a three-day period is about 43 per cent, but actually 41 per cent of onsets occurred during Monday to Wednesday, and 45 per cent during Thursday to Saturday. Since this effect is more evident in the two more reliable groups, and less evident in the least reliable group, it is hardly likely to be due to a systematic error in the recording of the data. The few married women (19) in Group IA gave 132 onsets on Mondays to Wednesdays, and 125 on Thursdays to Saturdays, so that the weekly periodicity cannot possibly be due to them.

In interpreting this result, it must not be forgotten that the dates are not wholly independent. Thus each woman supplied a number of dates, and a woman who had a 28.0-day average would always tend to start to menstruate on the same day of the week. The fact that three separate batches of women show the effect is evidence against this being the whole cause of the result. The effect is so small, however, that little importance can be attached to it in the absence of confirmation from quite independent sources.

(*b*) *Lunar Periodicity.*

There are several kinds of lunar month. The most familiar is the synodical lunar month, during which the moon goes through the phases of new to full and back to new; this month varies in length by about 12 hours, and it averages approximately 29.53 days. The other kinds of lunar month are unfamiliar to those not having any special astronomical knowledge, and so could not have a general psychological effect. Indeed, the average town-dweller is hardly even aware of the phases of the moon. Some of the other cycles are the tropical lunar month (27.32 days), the sidereal lunar month (27.32 days), the nodical lunar month 27.21 days), and the anomalistic lunar month (27.55 days). The data were examined in relation to each of these, and the methods used can be indicated sufficiently in the case of the synodical lunar month. The average duration in this case can be taken as $29\frac{1}{2}$ days, for at the end of the 22

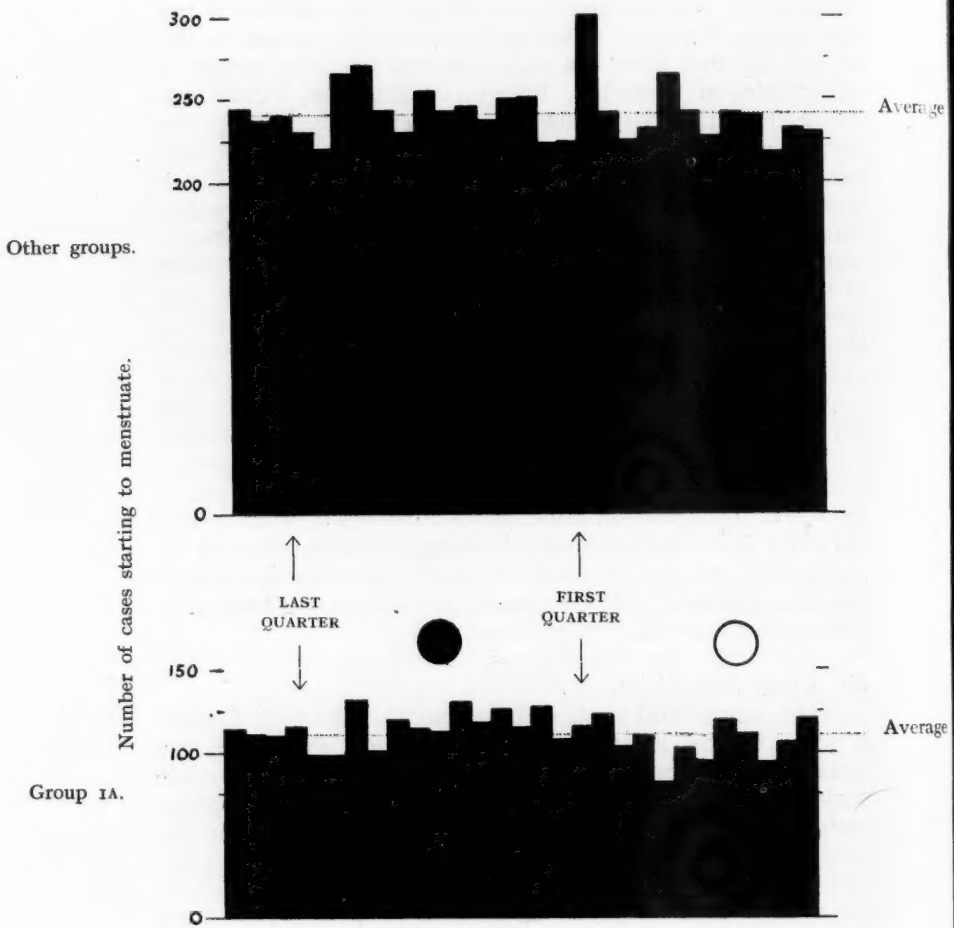

FIG. 5. Lunar periodicity (synodical month). Note that the apparent rhythm in Group 1A cases is not confirmed by the remaining groups. There is no statistically significant synodical lunar periodicity. See pp.

months of the investigation this causes an error of only about half a day. Two such months will, therefore, last 59 days. The numbers of women starting to menstruate on successive days were written down in horizontal rows of 59, just as they were put down in rows of 7 in the investigation of weekly periodicity, so that the women starting a period at full moon, for example, came nearly into the same vertical column. There are two cycles in the 59 days, and one was fitted below the other so as to accentuate any effect which might be present. The vertical columns were then added, and the numbers plotted into a figure, so that any considerable periodicity could be seen at a glance (Fig. 5).

Fig. 5 gives the results of these operations. In both parts of the figure there are considerable irregularities; but for the IA group it looks as if there is a trough lasting about a week just before full moon, and a series of frequencies above the average for about a week after new moon. The two other groups do not confirm this suggestion. Nevertheless, the χ^2 test was applied to the data. The deviations from the average daily frequency are not greater than would often occur by chance.

Further, when the days are grouped together in threes, fives, and sevens, so as to show up the slightest rhythm, the deviations are still not significant. Such grouping gives a minimal value of p of 0.07 for Group IA, but much higher values for the other batches, and for all the data together. Consequently, if there is a synodical lunar rhythm, it is so small as to be hidden by the random variations, even with over 10,000 dates.

The tropical lunar month was tested in the same way, with an even less significant result, the lowest value of p obtained being 0.10. Since Arrhenius[33] found a tropical lunar rhythm, it is necessary to examine his data to see if there is any reason for the discrepancy between his conclusion and ours.

Arrhenius[33] used the case-records of 11,807 women who had been patients in two lying-in hospitals in Stockholm, Sweden, between 1848 and 1897. On entry, each woman was asked the date of onset of her last period, which had taken place some 6 months or more earlier. The reply given must often have been quite inaccurate, and in the form "early in June", "the middle of April", and the like; so that for the 10th, 15th, and 20th of the calendar month the frequencies were 420, 723, and 528 respectively, while for the 11th, 16th, and 21st they were 114, 221, and 118 respectively. Arrhenius was aware of this (his table on p. 379), but he considered that he could overcome the

deficiencies of the data by a statistical smoothing process. His data and the smooth curve fitted to them by a Fourier method are shown in Fig. 6, together with our data. On the curve, the maximal and minimal values are only about 7 days apart, while it will be seen from what has been said above that many of the dates are likely to be in error by at least a week. Further, the errors are not random but systematic, for there are very big maxima on certain days in the calendar month. Consequently, Arrhenius's curve can be regarded as showing the frequency with which these days (10th, 15th, 20th) coincided with the passage of the moon through Aries, and so on, rather than showing any relation between menstruation and the tropical lunar month.

Arrhenius's data are thus gravely deficient in reliability; and the form in which they were collected could be responsible for the rhythmical appearance. Our data are about the same in number (10,416): they are far more reliable than his, and they do not show any tropical or any other lunar rhythm.

Another conclusion arrived at by Arrhenius was that the average interval between menstruations is about the same as the length of the tropical lunar month. His average was derived from data collected by Hannover,[38] in which the interval was usually given in whole weeks (compare Section II*a*), so that it is of very little value. Moreover, even if one collection of women were to give an average of exactly 27.32 days, another collection having a different age distribution would probably give a different average (see Section VII*b*).

We cannot, therefore, find any justification whatever for associating the date of menstruation or its rhythm with lunar phenomena.

IX. Discussion.

We are unable to support many of our conclusions by reference to the literature, because none of the data so far published has been analysed as ours have been. Indeed, most of the accurately described groups of cases are too small to permit of such analyses. Hartmann,[39] in an accurate scientific study of menstruation in the rhesus monkey, correctly states that "we know almost nothing about the physiological variations in the menstrual phenomena of women." The analysis of menstrual data is difficult and requires exact statistical handling. This may have deterred other investigators, and we have, therefore,

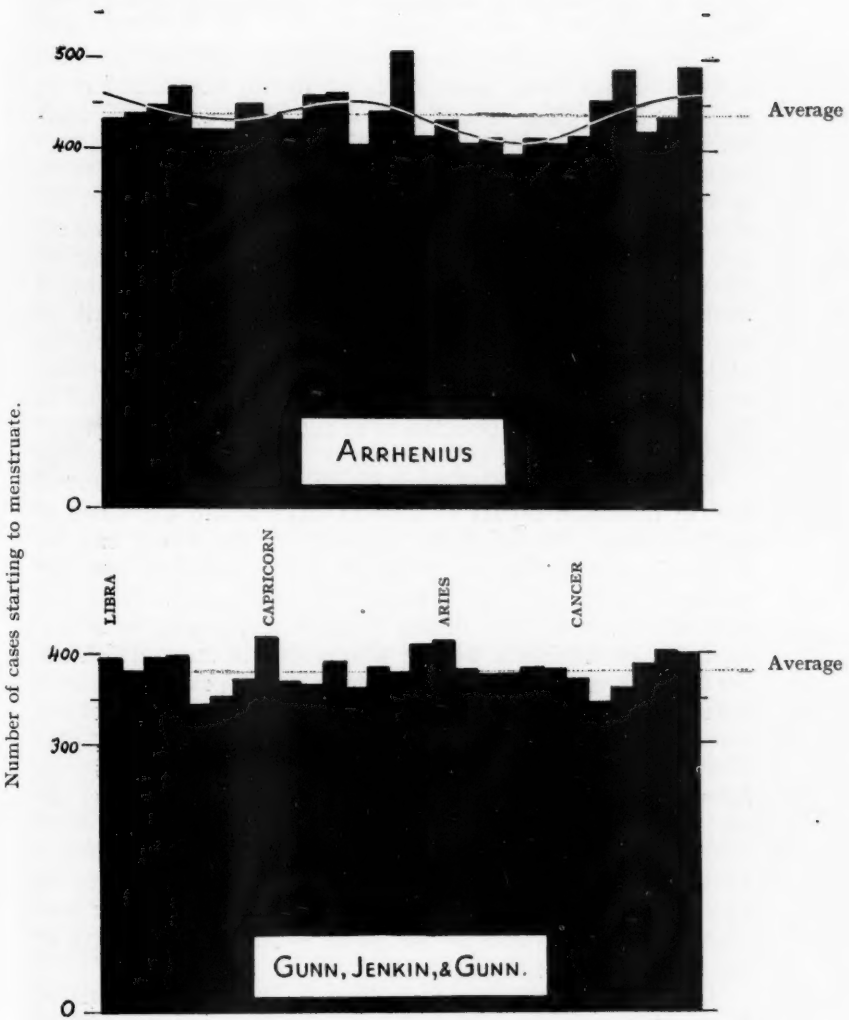

FIG. 6. Lunar periodicity (tropical month). The upper part of the figure represents the data of Arrhenius[33] and the smooth curve which he fitted to them; the lower part shows our data. Arrhenius's curve certainly does not fit our data. There is no statistically significant tropical lunar periodicity.

given in appendices, examples of our methods of dealing with the figures.

The large variations in the menstrual intervals of most normal women have been indicated by all the recorders of accurate data. The information about these variations finds several applications in current practice. It is evident that gynaecologists should abandon the use of the word "type", with its presumption of a regularly recurring interval. In its place, the gynaecological history should make such statements as "menstrual records show an interval of 24–29 days, averaging 26 days" or "the patient states that menstruation occurs every 4 weeks". Unless the patient has kept records for at least 12 months, any attempt to describe the interval in days is entirely misleading. The fallibility of menstrual histories probably explains some of the inconsistencies which have been found in the past between the appearances of endometrial curettings and the menstrual history.

Knaus's[3] experimental work seems to show that in normal women ovulation occurs exactly 14 days before the onset of menstruation. According to this author, the ovum can be fertilized only during the 24 hours after ovulation, and the spermatozoa become inert within 2 days of emission. Thus conception can occur only during 3 days in any one menstrual interval. He advises a woman who wishes to know which are her fertile days and which her sterile to keep an exact menstrual calendar for a year; she will then have some knowledge of her variations and will be able to make some prediction of the date of ovulation. If, for example, she finds that her intervals vary from 26 to 28 days, then ovulation may occur in future intervals on any days from the twelfth (26 minus 14) to the fourteenth (28 minus 14). The spermatozoa may live for 2 days before ovulation and the ovum for one day after; and so, with an additional day before and after as a margin for error, her possible fertile days would be the ninth to the sixteenth days of her intervals.

Our results show that a variability so low as that postulated in the example above (26 to 28 days) is rare indeed; and 84 per cent of our cases had a range of at least 6 days. The typical range was 8 or 9 days. Taking a fairly typical example, with menstrual intervals varying from 25 to 33 days, the possible ovulation time would vary from the eleventh day to the nineteenth, and the sterile days would fall before the eighth day and after the twenty-first. Allowing 6 days for menstruation,

the possible fertile days would be 13 in number, and the sterile ones would be the seventh and from the twenty-first to the onset of the next menstruation.

An increase in the length of Knaus's possible fertile period has been suggested by Latz[40] and by Holt,[27a] on the basis of a large number of records of sexual intercourse. Holt, using intermenstrual pain as an indication, concluded that the time from ovulation to the beginning of the following menstruation varies by 2 days on either side of Knaus's 14 days, but he agrees with Ogino[41] and Knaus in saying that it is this time rather than the time from menstruation to ovulation which is relatively constant whatever the length of cycle. Holt takes the view that a single exceptionally short or long interval ("anticipated" or "delayed" menstruations) may be due to external factors operating after ovulation has taken place, and that such an exceptional interval can be neglected in estimating the fertile days. He sets out certain principles for the guidance of medical advisers, and he states that they have been found satisfactory in practice. He does not make Knaus's allowance of a day before and after ovulation as a margin for error, but allows 2 days before and after for variation in the time from ovulation to menstruation. In the example given above, he would allow for 15 days of possible fertility instead of 13, so that in what we believe to be a fairly typical case, the safe period would be from the twenty-second day to the following menstruation.

In the light of our results on the variability of the menstrual interval, it is clear that the safe period method of contraception is not wholly satisfactory for everyone as a sole method (cf. Young[14a]). It should be of great value in some cases and of some value in most cases. In any woman, an unusually early or late menstruation, quite normally correlated with ovulation, may occur at any time, and a single such occurrence may result in undesired pregnancy. On the other hand, if pregnancy is desired with the minimum of sexual intercourse or in the minimal number of months, concentration on the days surrounding the usual time of ovulation is a useful method of accomplishing this purpose. In any case, predictions cannot be made without an accurate series of menstrual records, preferably covering at least a year; and our results show that conclusions from annual records should be amended from time to time as the age of the subject increases.

We have adopted two distinct measures of the variability of an individual. One is the difference between the shortest

interval and the longest (D.S.L.), and the other is the mean deviation (M.D.). The D.S.L. is normally determined by *unusual* circumstances, the occasional very short and very long intervals, and it does not give any direct indication of the usual variation. In a few cases, if a single exceptional interval is not counted, the D.S.L. falls to a quarter of its previous value. A further year's records would be likely to yield another exceptional interval, so raising the D.S.L.; no amount of subsequent regularity will ever reduce it. Nevertheless, this measure of variability has its value, for example, in connexion with Knaus's method of contraception, when the exceptional interval may be very important. On the other hand, the M.D. is constantly corrected both upwards and downwards as the time covered by the records increases. Consequently, the longer the time of the records, the larger the D.S.L. will be, both absolutely and compared with the M.D. It is, therefore, the M.D. which should be used as a measure of variability in comparing results of different workers whose records cover different periods of time.

Jolly[2] cites evidence to show that some of the cyclical sexual changes, of which menstruation is one, go on during pregnancy. He takes the view that birth tends to occur at a definite point in one of the concealed cycles, namely, in the short-interval cases, the time when the eleventh missed menstruation would normally have occurred. The prediction of this date is, therefore, a matter of some interest.

If there were women who menstruated regularly every 24 days, we could predict the dates of their future menstruations with ease; but Jolly's assumption that such women exist is almost certainly incorrect. Nevertheless, if we know sufficient about the last dozen or so menstrual cycles, we can state the probability that a future menstruation will start between certain fairly close dates on the assumption that there is no new major factor affecting the periodicity (Statistical Appendix III). It is not improbable that pregnancy itself is such a factor.

A comparison between past menstrual intervals and the duration of pregnancy could verify Jolly's theory only if this assumption happens to be correct. What is clearly needed now is some test to reveal the sexual cycle during pregnancy. An investigation using such a test in connexion with accurate data of overt periodicity and length of gestation would examine both Jolly's theory and its basic assumption, and might also reveal other correlations.

By establishing the fact that the length of each menstrual

interval is independent of the length of its predecessor, we have made an addition to the knowledge of the cycle which is a necessary preliminary to any study of the causes of variations.

We did not find any variation in average menstrual interval in relation to occupation. Had our cases included substantial groups of factory workers, waitresses, chorus girls, leisured women, and so on, the result might well have been different; it would certainly have been more valuable.

Our results make it probable that as a woman grows older her menstrual interval tends to shorten. This is a new observation for which we can find little support in the literature. Such a variation with age nullifies comparisons between our cases and other cases for which the age-distribution is not suitably stated. Engle and Shelesnyak[24] found an average cycle of 33.9 days in 100 adolescent girls. Had they worked out the average by our method, their figure would have been still higher, for it would not have been weighted by the larger number of shorter cycles. Our youngest women (aged about 20, cf. Table V) gave a mean of the individual average intervals of 30.1 days, so that the work of Engle and Shelesnyak suggests that the decrease in interval starts early in life, and is greatest at that period.

Marriage appears to have little or no effect on the periodicity.

Many women state that their menstrual intervals are longer during the cold weather. Our results show that such an effect is certainly not the rule.

This work originated in discussions between Dr. C. Amirthalingam and one of us (D. L. G.); Dr. Amirthalingam would have continued to take part in it had he not left the country before the collection of the data was completed. We have availed ourselves freely of assistance from many people and we wish to record our thanks to them. Professor Sir Harold Beckwith Whitehouse has been interested and helpful from the beginning; he sponsored the work and obtained from the Research Committee of the University of Birmingham the considerable grants necessary. We also thank especially Professor R. A. Fisher, F.R.S. (statistics), Dr. A. M. Bidder, Dr. Barbara Gunn, and Dr. L. R. Bishop (analysis), Professor H. Munro Fox, F.R.S. (lunar periodicity in animals), and James Young, Esq., F.R.A.S. (astronomical data).

We hope that the results presented here will in part discharge our indebtedness to those many people who sent us addresses or records, and we wish to thank them, particularly the 209 whose information was placed in the first class.

X. Summary.

1. Menstrual data have been collected from normal women by a postal method in which tests of reliability were possible.

2. The 770 women providing periodicity data were divided into (*a*) 209 reliable cases, (*b*) 270 fairly reliable, and (*c*) 291 unreliable. Many of the best 472 cases recorded in the literature would fall into (*b*), so that we have probably doubled the number of first-class records available.

3. We find that 90 per cent of cases had an average interval between the onsets of successive menstruations lying between 25 days and 36 days inclusive, 3 per cent had an average of 37 days or over, and 7 per cent of less than 25 days. Only about 2 per cent had an average of less than 24 days. The average interval did not show any predilection for whole weeks. The average for all cases in section (*a*) and (*b*) (479 cases) was 29.0 ±0.19 days; the commonest averages lay between 26.0 and 29.0 days.

4. No cases were found which did not vary by at least 2.75 days between the shortest interval and the longest. The typical difference between the shortest interval and the longest (D.S.L.) was 8 or 9 days; the difference was 6 days or more in 84 per cent of the women, and over 13 days in 30 per cent of them.

5. The lowest mean deviation of the separate intervals from the individual average was ±0.6 days. About half the women had mean deviations of ±2 days or less, and the other half of ±2 days or more. In 5 per cent of women the mean deviation was over a week. The term "regular" has no precise meaning in connexion with menstruation.

6. The duration of one interval is not influenced by the duration of its predecessor.

7. Among the professional classes which we sampled a correlation between occupation and average interval was absent. Marriage did not appear to affect the periodicity.

8. There was a progressive decrease in the average interval with increasing age amounting to one day in 5 or 6 years.

9. There was no tendency for the interval to vary with the seasons of the year.

10. There appeared to be a slight tendency for menstruation to start in the latter part of the working week.

11. No connexion whatsoever could be detected between menstruation and the moon in the data of over 10,000 menstruations. The approximate coincidences, which are so well known, appear to be fortuitous.

12. The bearings of our results on a method of control of conception and on prediction of birth date are discussed.

XII. Statistical Appendix I.

General Statistical Methods.

Many measurable attributes of the individuals in a population are normally distributed. An approximately normal distribution is shown in Fig. 3. This figure summarizes the available information about the frequencies of the various lengths of interval in the 25-day cases. It is often convenient to have still shorter summaries. The shortest of these is the average, the sum of all the separate intervals in days divided by the number of intervals $\left(\bar{x}=\frac{\Sigma x}{n}\right)$.

The average alone does not tell us anything about the scatter of the items (i.e. the separate intervals)—that is, whether most of them are very near the average, or many of them far from the average. This is represented in the figure by the width of the diagram. The simplest measure of scatter is the arithmetic *mean deviation* (M.D.). The difference between the average and each individual item is worked out, all these differences are added together irrespective of whether positive or negative, and the sum is divided by the number of items $\left(\text{M.D.}=\frac{\Sigma(x-\bar{x})}{n}\right)$. This measure of scatter has been used in our estimate of the regularity of menstruation because it is short to work out and easy to understand.

Another measure of scatter is the standard deviation (S.D.) or root mean square deviation. The differences as found for the M.D. are squared, the squares added together and then divided by the number of degrees of freedom ($n-1$, i.e. one less than n, the number of items), and the square root of the result is found $\left(\text{S.D.}=\pm\sqrt{\frac{\Sigma(x-\bar{x})^2}{n-1}}\right)$. The S.D. is usually about 50 per cent larger than the M.D. The S.D. is more valuable than the M.D. because it can be used in tests of the reliability of the average and so on.

The larger the sample we take the more nearly is our average likely to approximate to the real average of the whole population—i.e. the more reliable the average found is likely to be. If a sample consists of few individuals, the average will be un-

reliable. Another sample is then likely to give a very different average. A convenient measure of the reliability of the average is the standard error (S.E.). This is the S.D. divided by the square root of the number of items $\left(\text{S.E.} = \frac{\text{S.D.}}{\sqrt{n}}\right)$. It is the S.E. which usually follows an average—e.g. 23.47 ± 0.34 days.

If the distribution is approximately normal, the S.E. can be used to tell us the probability that the average is in error by certain specifiable amounts. Tables have been constructed for this purpose. If a reasonably large number of items (over 30) is used to find the average, it can be said that in 31.7 per cent of samples, similar to the one in question, the average will differ from 23.47 by ±0.34 days or more; in 4.6 per cent of samples the average will differ by ±0.68 days or more (=2S.E.) from 23.47 days (Ezekial).[42] Alternatively, from a similar table in another form (table of t, Fisher[37]), we can say that 20 per cent of samples from the same population are expected to yield an average differing from ours by $\pm 1.28 \times 0.34$, i.e. by ±0.44 days or more, and so on. The remaining 80 per cent of similar samples are expected to have averages differing by less than ±0.44 days from 23.47.

With the aid of such figures as these, the S.E. can be used to compare two averages, to see if the difference between them is likely to occur by chance even if they are derived from two samples from a homogeneous population. If the difference is unlikely to occur by chance, it suggests that our sampling is not random, or that we have really sampled two distinct populations, instead of one, or something of that kind (see Statistical Appendix II).

Statistical Appendix II.

Comparison of Two Averages.

Suppose we want to compare two averages, to see if the difference between them is likely to be due to chance. If the difference can be ascribed to chance, we have no indication of a real difference between the two populations which have been assessed by the averages of the two samples. Thus from Table II, the woman in case No. 2875 has an average interval of 27.66 days ±0.22, and case No. 2159 of 23.47 days ±0.34 days. The difference between the two averages is thus 4.19 days. The S.E. of this difference is less than the sum of the two separate standard errors, and is found by taking the square root of the sum of their squares.

S.E. of difference $= \pm\sqrt{0.22^2+0.34^2} = \pm 0.40$.

The difference (4.19 days) is thus over ten times its S.E. ($\pm$0.40 days). Entering the table of t (Fisher) at $n=29$ (the sum of the degrees of freedom of the separate standard deviations), we see that a difference so much bigger than its S.E. is so unlikely to occur by chance that it is not in the table at all. We may, therefore, regard these two women as having significantly different periodicities. Indeed, a difference of one day would be significant with cases showing this degree of variability. The result of this test, then, is in line with our general conclusions on the data of Table III.

Statistical Appendix III.

Estimation of the Date of a Future Menstruation.

Suppose that we wish to estimate the date of onset of some future menstruation in the woman in case No. 2159. Because of its interest in connexion with Jolly's theory, take the eleventh menstruation in the future. We must assume that there will not be any striking change in the periodicity. The further assumption that there is no correlation between successive intervals is justified in Statistical Appendix IV. If the periods were to recur quite regularly at the average value, the eleventh one would start 11 times 23.47 days after the recent one, i.e. 258.17 days after it. Owing to the variability it is very probable, in fact, that it will fall a certain time before or after that. We can estimate the value of the probabilities.

If the periods go on much as before, the general variability of the case remaining much the same, the S.D. of the 11 future intervals will be $\pm$1.41, the same as the S.D. for the past 17 intervals. Consequently the S.E. of the average of the future 11 intervals will be $\pm$1.41 divided by $\sqrt{11} = \pm 0.42$ days. We do not know what the average of the 11 future intervals will be, but the S.E. of this average should be $\pm$0.42. Now we know that the S.E. of the average (23.47 days) of the past 17 intervals is $\pm$0.34 days. Consequently, whatever the average of the 11 intervals, the difference between it and the known average will have an S.E. of $\pm\sqrt{0.42^2+0.34^2} = \pm 0.54$ days. Entering the probability table (Eezkial[42]) at $n=16$, the number of degrees of freedom of the actual observations, we find that $p=0.333$ for a difference equal to or greater than the S.E. That is to say, there are 33.3 chances in 100 that the past and future averages will differ by $\pm$0.54 days. Similarly, there are about 6 chances

in 100 ($p=0.064$) that they will differ by twice the S.E. or more. Taking the latter as a fairly small probability, 15 to 1 against, if the averages differ by $2 \times \pm 0.54$ days $= \pm 1.08$ days, then the sum of 11 intervals will differ by 11 times as much. There is, therefore, betting of 15 to 1 against the total of 11 intervals differing by $11 \times \pm 1.08$ days or more (i.e. about ± 12 days) from the 258 days originally reckoned.

It is clear, then, that we cannot estimate the date of the eleventh future period with any great accuracy, even in such a regular case as this one (M.D. $= \pm 1.0$ days). The chances are about 15 to 1 against the period starting outside the limits of 246 to 270 days after the recent one, and about 2 to 1 for the limits 252 to 264 days. This is of no value in fixing the date of a holiday, but the method is of interest in connexion with Jolly's theory. The proper tests for that theory are indicated in the body of this paper.

Statistical Appendix IV.

Test for Correlation Between Successive Intervals.

It is not intended that this appendix should be understood by the general reader. It is necessary, however, to place on record the methods used.

If there are n intervals in a particular case, the first $n-1$ intervals are put down as a column of x, and the last $n-1$ as a column of y. $\bar{x}$ and $\bar{y}$ are the averages of x and y respectively. The sum of $(x-\bar{x})y$ and the sum of $(x-\bar{x})^2$ are worked out for each case, and for the first 30 cases of Group 1A the following expression is evaluated, giving the correlation b.

$$b = \frac{\Sigma S(x-\bar{x})y}{\Sigma S(x-\bar{x})^2}$$

For the first 30 cases in Group 1A, $b = -0.0123$. The correlation is very small indeed.

Significance is tested by the expression

$$\sqrt{\frac{b\Sigma S(x-\bar{x})y}{\frac{\Sigma S(y-\bar{y})^2 - b\Sigma S(x-\bar{x})y}{n}}} = 0.22$$

The correlation found would be very likely indeed to occur by accident.

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Granulosa-Cell Tumours of the Ovary.

A Review of the Literature.

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Introduction.

THE first description of the tumour which subsequently became known as the granulosa-cell tumour of the ovary is usually stated to be that of von Kahlden[1] in 1895. He called this tumour an "adenoma of the Graafian follicle, with transition to malignancy." His description of the tumour and his diagrams were extremely good, but unfortunately he did not give any information regarding the clinical history, save that the tumour was removed "from a young girl." Interest in such tumours has gradually been increasing since that time. Some of the early reports of tumours said to be of the von Kahlden type were probably malignant neoplasms of other types which had been incorrectly diagnosed.

It is sometimes considered that the ovarian tumour described by Rokitansky in 1855[2] as one in which cysts resembling follicles were found was the first report of a granulosa-cell tumour, but the view generally held is that the von Kahlden tumour was the first typical granulosa-cell tumour.

Acconci in 1890,[3] Emanuel in 1893,[4] Voigt in 1903[5] and Liepmann in 1904,[6] described tumours in which follicle-like areas were found. These cases are occasionally referred to as being early reports of granulosa-cell tumours, but they are probably cases of other types of primary or secondary ovarian carcinoma.

A tumour which is usually included in the literature of granulosa-cell tumours was described by Gottschalk in 1902[7] as "folliculoma malignum ovarii." At the time, Pick[8] stated that he considered the tumour in question to be struma of the ovary developing in a teratoma. This tumour is again discussed by Taussig,[9] writing in 1931. Taussig, who had the opportunity of working with Gottschalk at the time he described the folliculoma

malignum ovarii, here voices his agreement with Pick. His opinion is of value for he had the opportunity of examining this tumour, later described as a granulosa-cell tumour, and has maintained an interest in the matter ever since. It would seem to be safe, on the evidence, to exclude Gottschalk's tumour from the literature of granulosa-cell tumour.

The tumour described by von Mengersheusen[10] in 1894 as "adenocarcinoma folliculare ovarii" was quite probably a granulosa-cell tumour, and if so this is the first one reported, being described a year before the von Kahlden tumour.

In 1904, Polano[11] described four cases of ovarian tumours which he called "pseudoendotheliomata." These cases are also sometimes erroneously considered to be early reports of granulosa-cell tumours.

An ovarian tumour described by Orthmann[12] in 1899 was probably the next true granulosa-cell tumour to be described after von Kahlden's case.

Schröder[13] in 1901 reported a tumour of the von Kahlden type in a patient aged 36. This patient was known to be well two years after operation for the removal of the tumour.

In 1902, Fothergill[14] reported two cases of ovarian tumours which seem to be undoubted examples of the "oöphoroma folliculare" later described by Brenner.[15] Fothergill evidently considered these tumours to be malignant, but did not give any after-histories. He referred fully to previous descriptions of ovarian tumours containing follicle-like areas, some of which, as has already been mentioned, are not now considered to be examples of the granulosa-cell tumours.

In 1907, Ingier[16] described two cases of ovarian tumours of follicular origin; Brenner[15] described three cases, and Blau[17] also reported a tumour of the von Kahlden type.

By this time the nomenclature was becoming involved, and different names were being given to tumours of this group according to the views of their investigators. Orthmann had described such a tumour as "fibroma papillare superficiale carcinomatosum ovarii." Schröder described follicle-like areas in the tumour, and, according to Fothergill,[14] stated that the term "folliculoma" could be applied to all such cases. Fothergill[14] did not give any name to the tumour, but pictures of the first of his two cases were sent to Orthmann, who described them as "carcinoma ovarii", and to Schröder, who gave them the name of "fibro-adenocarcinoma". Brenner[15] chose the name "oöphoroma folliculare" for the tumours he described.

There was thus not any general concurrence of opinion as to the correct appellation of this rare tumour, and when, in 1914, von Werdt[18] proposed the name "granulosa-cell tumour of the ovary", this accurate and convenient descriptive term was accepted, and has remained in use ever since.

Tumours of the type described by Brenner[15] in 1907 as "oöphoroma folliculare" have been included by the majority of authors as granulosa-cell tumours, or described as closely allied tumours, but have been rejected by a few authorities, notably by Robert Meyer.[26] The term "follicle-cell tumour" of the ovary, or "folliculoma" as suggested by Schröder[13] in 1901, would include tumours of the Brenner type and granulosa-cell tumours, and would be both accurate and simple. In this paper the term "granulosa-cell tumour" is retained, and the oöphoroma folliculare is described as a variety of granulosa-cell tumour.

Up to the present time I find that about 200 cases of granulosa-cell tumour have been described in the literature. Interest in the tumours and publications regarding them have increased greatly during the last 10 to 15 years, and more of them are being recognized. The granulosa-cell tumour is, however, undoubtedly a rare ovarian tumour.

Writing in 1930, R. W. Te Linde[19, 20] made a very valuable contribution to the literature of the granulosa-cell tumour, in a paper describing 4 cases of his own, and reviewing clinical reports of tumours described by other authors. He was able to show that in most of the cases in which the after-history of the patients was available, it was evident that the tumours were not malignant, local removal being followed by complete cure.

Until this time the tumours had been generally considered to be malignant, this opinion being held on the grounds of histological appearances. Brenner,[15] however, had stated in 1907 that he considered the tumours which he described to be innocent. He had no after-histories to support his opinion, for one patient died of intestinal obstruction 8 days after the operation, and the other two tumours were accidental findings at autopsy.

Since Te Linde's papers[19, 20] were published, information has gradually been increasing to show that it is indeed a fact that the histological appearance of the granulosa-cell tumour is not entirely a true guide to its clinical characteristics, and that many, if not all, of the granulosa-cell tumours recognizable as such are not malignant.

E. H. Lepper, A. H. Baker and D. M. Vaux[21] in 1932 reported 7 cases of granulosa-cell tumours collected over a period

of 19 years at the Elizabeth Garrett Anderson Hospital. All the patients were at the time alive and well, at periods of 11 months to 15 years after the operation. I am permitted by these authors to state that in a recent follow-up of these patients, all except one were still alive and well. This patient died at the age of 73, 17 years after removal of the ovarian tumour, the cause of death being carcinoma of the stomach and cardiac failure. When examined a few days before death, there was not any evidence of a pelvic tumour. An autopsy was not obtained. The longest after-history was 17 years after operation. The operation in this case had been only salpingo-oöphorectomy.

Certain authors, notably H. O. Neumann,[22] and Emil Novak,[23] have continued to call such tumours granulosa-cell carcinomata, although in some of their own cases in which the after-histories have been obtained, the tumours have been shown to be not malignant.

The fact that granulosa-cell tumours of the ovary have a decided action upon the sexual functions of the patient has long been recognized. When they occur before puberty they give rise to precocious puberty; in the period of active adult sexual life they cause disturbances of the menstrual function; and after the menopause they cause post-menopausal uterine bleeding.

In recent years the widespread interest in endocrines in general has also been extended to these tumours. Evidence is now accumulating to show that they produce the oestrus hormone oestrin, and this endocrine activity probably accounts for their effect on the sexual life.

This paper is an attempt to summarize the literature into a form which may be useful to anyone who wishes to obtain a general idea of the subject; to correlate the clinical and histological pictures of this tumour; and to show that it can, in most cases, be diagnosed before operation.

Morbid Anatomy.

The macroscopic appearance of the granulosa-cell tumour is of great importance, because the opinion of the surgeon as to its nature will guide him in deciding upon the extent of the operation which he will perform for its removal.

The typical non-malignant granulosa-cell tumour is a unilateral ovarian tumour, which may or may not be associated with another benign ovarian tumour in the same ovary.

There is considerable variation in the size of granulosa-cell tumours. Very small tumours have been described, which are so

small as not to cause any visible ovarian swelling, but which can give rise to characteristic symptoms. Schiller,[24] in his comprehensive work on granulosa-cell tumours, describes a granulosa-cell tumour measuring 8 x 6 x 5 mm. which occurred in the ovary of a woman of 60 years of age. The patient had post-menopausal bleeding caused by this tumour. The uterine endometrium showed typical thickening.

Te Linde[19, 25, 20] described a granulosa-cell tumour of 3 mm. diameter. It occurred in the hilum of the ovary. The patient was a woman of 43, who had had severe uterine bleeding, but the presence of many fibroids in the uterus, such as were found at the operation in this case, would alone have been able to account for the symptoms.

The largest granulosa-cell tumour yet described was in another case reported by Te Linde.[19, 25, 20] The tumour was 30 cm. in diameter and weighed 20 pounds 4 ounces. In this case the patient, aged 50, suffered from post-menopausal bleeding, and was well 2 years after the operation for local removal of the tumour.

The typical granulosa-cell tumour is an encapsulated growth, the capsule being smooth, firm and fibrous. It is not adherent to the surrounding parts. The capsule may vary in thickness in different places, a finding which is probably due to thickening of the capsule occurring in areas in which friction between the tumour and neighbouring organs has taken place. The tumour is not, as a rule, lobulated.

The blood-supply to the tumour is rich, and large vessels may be seen upon the surface. On section, the tumour is found to be of soft solid consistence, or, more commonly, partly solid and party cystic. The colour of the tumour is often bright yellow, about the colour of a ripe corpus luteum. Some tumours have a pinkish fleshy colour, as described by Te Linde.[19, 20] This pinkish ground tissue may contain bright yellow flecks. The yellow colour of the tumours and their vascularity present a striking picture, especially when torsion of the tumour has occurred, and has caused haemorrhage into the tumour's substance. The consistence and appearance are frequently considered suggestive of sarcoma of the ovary. It is rare to find a friable tumour. It is significant that necrosis and inflammatory change are rare, unless torsion has occurred. This is in sharp contrast to the findings in malignant tumours, in which necrotic change is common. The cysts which are seen on the cut surface vary in size from about a pin-point to several centimetres in

diameter. They are smooth-walled and filled with clear or blood-stained fluid.

The occurrence of another innocent tumour in the same ovary as one which contains a granulosa-cell tumour is by no means rare. Te Linde[19, 20] states that this association is infrequent, but he is not supported in his statement by other authors. Association with ovarian fibroma is common. According to Schiller[24] this is due to a common mesenchymal origin of both tumours.

Multilocular pseudomucinous cysts and unilocular ovarian cysts are not infrequently found in association with granulosa-cell tumours. In such cases the granulosa-cell tumour is found as a solid area in the cyst's wall, and its nature may not be suspected until sections of this part of the tumour have been cut. Robert Meyer[26] describes their occurrence with dermoids, and Schiller[24] states that they can occur with teratomata.

I have had the opportunity of examining the seven cases of granulosa-cell tumours reported by Lepper, Baker, and Vaux,[21] and one case of Miss E. Bolton, referred to later, and it is interesting to note that in every case the ovary affected was completely replaced, either by the granulosa-cell tumour alone, or by this tumour and its associated tumour. This point is not made in the literature on the subject.

Tumours which are described in the literature as malignant granulosa-cell tumours of the ovary are usually bilateral, often show extension of the tumour to the Fallopian tubes, broad ligament, or uterus, and are associated with peritoneal metastases. It is very probable that many of the tumours so described are not in reality malignant granulosa-cell tumours, but are examples of other types of primary or secondary ovarian carcinomata. The fact that many are bilateral is suggestive of their being metastatic carcinomata.

Histology.

Histology of the Follicle.

The histological appearances of the granulosa-cell tumour have been the subject of much discussion. It is probably true to say that interest has been somewhat unduly focused on the histology, in proportion to the interest taken in the macroscopic appearance of the tumour, and in the clinical history, particularly the clinical after-history of the patients. The multiplicity of growth-forms which occurs, and the association of different forms in the same tumour, have led to much confusion and to much

unnecessary complication in the classification of the histological pictures.

The understanding of the nature of the growth-forms is facilitated by the knowledge of the appearances of the various stages of the normal follicle. These are dealt with in great detail by Maximow,[27] and the following account is summarized from his work. In the primordial follicle, the cells surrounding the ovum are in a single layer and are oval or almost columnar in shape. Their nuclei stain lightly with haematoxylin, have a reticulated appearance, and are surrounded by clear acidophil protoplasm. As the ovum grows, the follicle cells surrounding it increase in number, and become cuboidal and then polyhedral in form. The cells in the layer immediately surrounding the ovum and those at the periphery of the follicle remain columnar and are radially arranged. The cells surrounding the fluid spaces of the normal follicle which are known as the Call-Exner bodies are also radially arranged, producing a rosette-like appearance. The membrana granulosa is the many-celled layer forming the lining the follicle when the fluid-filled follicular cavity has been formed. The cells composing it are known as the granulosa cells, and it is thus clear that they are the direct descendants of the follicular cells. The granulosa layer contains Call-Exner bodies. Honoré[28] considers these to be the result of active secretion by the surrounding granulosa cells, while Thomson[29] regards them as evidence of degenerative changes in the granulosa cells. He states that the starting-point of formation of fluid in a Call-Exner body is hydropic swelling of one or more granulosa-cells, and the swollen remains of the cells may often be recognized in the lumen of the Call-Exner body in its early stages.

Microscopically, the differences between the cells of the granulosa and those of the primordial follicle are that the granulosa-cells have less protoplasm than the primordial follicle cells; their nuclei stain more deeply with haematoxylin, but present the same shape and reticulated appearance, though their size is slightly less; and the cell borders are less distinct than those of the primordial follicle. After shedding of the ovum, the granulosa cells give rise to the true luteal cells.

Schiller[24] considers that the normal granulosa has a syncytial arrangement and that the cells only attain full epithelial characters when luteinization begins.

The connective tissue around the follicle forms a capsule surrounding the follicle, the theca folliculi. This later divides into two layers, the theca interna and the theca externa folliculi,

There is not a sharp limit between these layers, or between the theca externa and the surrounding ovarian stroma. The theca interna becomes vascular, and, after the ovum is shed, theca-luteal cells are formed from it, which resemble true luteal cells in all respects except size. They are smaller than true luteal cells. The theca externa retains its connective tissue character and forms a capsule to the corpus luteum.

Maximow[27] points out that the ovarian stroma cells should not be considered as common fibroblasts, because they have developmental potentialities, and, under the influence of hormones, can give rise to different cell types—to interstitial cells, and even to decidual cells in the rare cases of ovarian pregnancy.

Histology of the Granulosa-cell Tumour.

The existence of different cell-patterns in granulosa-cell tumours has greatly increased the difficulties of histological diagnosis. While it is necessary to be able to recognize the types of cells present in the tumours, it is just as essential to be familiar with the various characteristic cellular arrangements which may be found. Only by recognition of these characteristic patterns can the tumours be identified.

Division into three main types according to cellular arrangements is the method usually accepted in describing these tumours, though more intricate subdivisions have sometimes been described. Such extended classifications only confuse the subject more, and clarify it not at all. The three main types are: (1) the folliculoid; (2) the cylindroid or trabecular; and (3) the diffuse or sarcomatoid. Any or all of these types may be found in a given tumour. They are evidently closely connected, and Robinson[30] declares that they are all different stages in the same growth and that it is unjustifiable to separate them. He refers to the tumours as carcinomata, but gives as four characteristic findings the following points: (1) uniformity of the proliferating epithelium, especially in the early stages; (2) mitoses are rarely found; (3) infiltrative and destructive tendencies absent; and (4) the spread is by continuity and extension, and not by the lymphatic channels and blood-stream. These points are accepted as criteria of innocent, not malignant, tumours.

In the case of the oöphoroma folliculare, a type of granulosa-cell tumour which cannot be placed in any of the three main groups, association with any of the other three types of granulosa-cell tumour seems not to occur.

The stroma may be condensed around the epithelioid areas in these tumours, so as to form a theca. The theca has the appearance of smooth muscle-cells, but the fibrillae of the protoplasm are absent. Maximow[27] states that true smooth muscle-cells are, in fact, found in the theca interna of the pig's ovary. Smooth muscle-cells may also be found in the hilum of the ovary. In staining granulosa-cell tumours with Van Gieson's stain, this smooth muscle-like appearance of the thecal areas surrounding the epithelioid masses is frequently found.

(*a*) *The Oöphoroma Folliculare.*

The oöphoroma folliculare may be discussed first, as it probably corresponds to the primordial stage of the follicle. The structure of this tumour, as described by Brenner,[15] in 1907, is that of cell islets, many of which contain ova-like bodies placed centrally or eccentrically, embedded in the connective tissue stroma of the ovary. The islets may be circular or oval in shape, or of more irregular pattern. There may be one or two ova-like bodies in each islet, and the resemblance to ova is certainly very marked in many cases. It is now, however, generally accepted that this appearance is an expression of degenerative change occurring in the epithelioid cells. The acidophil degenerative fluid resembles the protoplasm of the ovum, and a separated degenerate epithelioid cell lying free in this fluid resembles the nucleus. The cells surrounding these ova-like areas are arranged radially. Robinson[30] is the only authority who still considers that such ova-like structures are the remains of true ova.

The cells of the oöphoroma folliculare are very similar to those of the primordial follicle. The nuclei are round or oval, staining lightly with haematoxylin, and with a reticulated appearance. The protoplasm is clear, acidophil, and occupies the greater part of each cell. The cell outlines are distinct. The shape of the cells in the body of the islets is round or polyhedral. The peripheral cells and those around the ova-like bodies are cubical or columnar, and are radially arranged. Mitoses are very rarely found. The stroma surrounding the cell-islets may be condensed so as to give the appearance of a theca, as in Fig. 1, which shows the typical appearance of the oöphoroma folliculare. This specimen was obtained from an ovarian tumour removed by Miss Muriel E. Landau at the Elizabeth Garrett Anderson Hospital (Case 7, Lepper, Baker and Vaux[21]). The patient, a woman aged 60, had

had irregular floodings for four months. The menopause was eight years previously. Three years ago there had been a slight vaginal haemorrhage for two days. At the operation, a movable left ovarian tumour was found. The uterus contained many fibroids. The right ovary and right Fallopian tube were normal. Panhysterectomy was performed with bilateral salpingo-oöphorectomy. The ovarian tumour replaced the ovary and was $3\frac{1}{2}$ inches in diameter. One-third of the tumour was solid, and studded with yellowish granules, and many minute cysts were just visible in the solid area. Fig. 1 shows the appearance of a section from the solid area. The other two-thirds of the tumour consisted of a tightly packed multilocular pseudomucinous cyst. The uterus was enlarged and the endometrium thickened, but the presence of several fibroids masks the effect the ovarian tumour might have had on the uterus. The patient was well and did not show any recurrence when examined 11 months after the operation.

The two cases described by Fothergill[14] in 1902 as ovarian tumours with ova-like bodies are very typical of oöphoroma folliculare. In his first case, the tumour, though unilateral, was adherent to surrounding structures, and the patient had lost weight, factors which are suggestive of malignancy. Ascites, not necessarily associated with malignancy in the case of ovarian tumours, was also present The adherence may have been accounted for by inflammatory changes due to a few attacks of subacute torsion of the pedicle. There is not, unfortunately, any after-history given with either of Fothergill's cases.

The illustrations of a case of Dougal in Blair-Bell's "Principles of Gynaecology",[31] and in Eden's and Lockyer's "Gynaecology",[32] are also typical of this tumour.

Herbert Spencer,[33] in 1926 described two cases which he called adenofibroma of the ovary. The drawings of microscopic sections from the second of these cases correspond to the pictures of oöphoroma folliculare. He stated that the first case was of the same type. One was in a woman aged 62, who was found to be well 16 years after the operation; the other occurred in a patient of 77, who had had a blood-stained vaginal discharge for four years. The patient died 11 days after the operation and autopsy was not obtained. Spencer referred to other similar cases reported by McNaughton-Jones,[34] Darwall-Smith,[35] and Arthur Giles,[36] in 1909. From an examination of the reports these appear to be typical cases of oöphoroma folliculare.

Te Linde's [19, 25, 20] Case 4, of a patient aged 62 who complained that her menses had never ceased, was one of oöphoroma folliculare. She was well when seen 12 months after operation; uterus, ovaries, and Fallopian tubes having been removed.

Though the oöphoroma folliculare is usually included amongst granulosa-cell tumours, Robert Meyer[26] describes it separately, and in his series of 33 cases of granulosa-cell tumour, fully reviewed by Habbe,[37] does not include a single tumour of this type. Robert Meyer[26] denies that this tumour has any sexual function; but Case 7 of Lepper, Baker and Vaux,[21] Case 2 of Spencer,[33] Te Linde's[19, 25, 20] Case 4, and others, show marked evidence of sexual function in post-menopausal haemorrhage and hyperplasia of the uterine endometrium. Brenner[15] considered the oöphoroma folliculare to be non-malignant, and it is usually agreed that this is so. In one of Brenner's cases the tumour was observed for four years, pre-operatively, and surgical interference was only decided upon when the tumour was found to be increasing in size. At the operation there was not any evidence of extension of the tumour. The patient died of intestinal obstruction eight days after the operation. Spencer's first patient,[33] who was well 16 years after the operation, may certainly be considered to be innocent. Te Linde's[19, 25, 20] Case 4, and Patient 7 of Lepper, Baker and Vaux[21] were both well 12 months after the operation.

Tumours of this type have been frequently described, and often diagnosed as adenofibroma or adenocarcinoma of the ovary. Ewing[38] classifies the oöphoroma folliculare with the malignant solid carcinomata of the ovary.

(*b*) *Remaining Types of Granulosa-cell Tumour.*

In these three types of granulosa-cell tumour, the cells, which are arranged in characteristic patterns, are of two types.

The first is the small round or oval cell, with a reticulated nucleus which stains deeply with haematoxylin, with acidophil protoplasm, and with indistinct cell-borders. The appearance of this cell corresponds very closely to that of the granulosa cell of the mature follicle.

The second type of cell more rarely found is the larger, polyhedral cell, the nucleus of which is larger than that of the granulosa cell. The nucleus of this cell stains deeply with haematoxylin, the protoplasm is more abundant, acidophil, and is limited by a distinct cell membrane. It is possible that this second cell corresponds to the very late stage of the follicle, or even to

the early stage of the corpus luteum. A few of the tumours described in the literature appear to be largely composed of true mature luteal cells, and should strictly be classed, not as granulosa-cell tumours, but as luteal tumours of the ovary.

The same characteristic patterns may be formed by each type of cell. It is usual to find a tumour composed wholly of one type of cell. The tumours are characterized by uniformity in size and staining capacity of their component cells and, when both types of cell are present in one tumour, as is sometimes found, they occur in different areas.

Mitoses in granulosa-cell tumours are rare, or altogether absent. It is difficult to be sure that this finding is reliable, since most pathological material is left outside the body for a few hours before fixing, during which time degenerative changes in the cells are sufficient to diminish the number of mitoses found. It is interesting to note that in a small granulosa-cell tumour, Te Linde[19, 20] found many mitoses, in a medium-sized one only a few, and not one in the biggest. He suggests that growth may be more active in smaller tumours, and less active in the bigger ones, where evidence of fibrosis and degeneration may be found, as in his case.

Although all three types of cell patterns may be found in any one tumour, one of them is usually predominant. The importance of making microscopic sections of several parts of the tumour may be stressed here. One section alone may fail to show any typical area, but further search should reveal appearances which are diagnostic of the granulosa-cell tumour. When possible, the use of large sections as a means of examining large areas of the tumour is extremely helpful.

The Folliculoid Type.

The folliculoid type of granulosa-cell tumour corresponds to the adenomatous areas described by von Kahlden,[1] and in the case he describes, cylindromatous areas were found in other parts of the tumour. The adenomatous appearance of the tumour is produced by the arrangement of the cells into larger or smaller epithelioid islets. The cells at the periphery of the islets, adjoining the stroma, have a marked radial arrangement, a feature particularly seen in the case of tumours formed by the larger type of cells. There is not any irregular invasion of the stroma. Within the radial edge the cells are arranged in rosettes, surrounding spaces filled with acidophil fluid, which probably correspond to the Call-Exner bodies of the growing

follicle and the mature granulosa, a resemblance which is well seen in the transition forms between the folliculoid and diffuse types of granulosa-cell tumours. They may be assumed to represent these bodies; and appear to be the site of formation of fluid by the cells, probably being a manifestation of cellular degenerative change. They sometimes have an ovum-like appearance and account for the finding of ova-like areas in these tumours, as in the oöphoroma folliculare.

Fig. 2 shows a folliculoid granulosa-cell tumour composed of cells of the smaller, oval type, and these are uniform in size. This tumour was removed by Miss Elizabeth Bolton at the Elizabeth Garrett Anderson Hospital, from a woman aged 48, who had been bleeding *per vaginam* fortnightly for 12 months, and previous to this had had eight years' amenorrhoea. Two weeks before admission to hospital the patient had had a severe attack of lower abdominal pain which lasted three days. A freely movable left ovarian tumour was found. Total hysterectomy and bilateral salpingo-oöphorectomy were performed. The ovarian tumour was $2\frac{1}{2}$ inches in diameter, and of soft solid consistence. The ovary was completely replaced by the tumour. Yellow patches were visible in the tumour's substance, and there had been effusion of blood into the tumour. The uterine endometrium showed a well-marked cystic hyperplasia. Microscopically, other parts of the tumour showed a cylindroid type of growth. The patient is well four years after the operation.

A case of S. B. Herd of folliculoid granulosa-cell tumour was mentioned as a malignant granulosa-cell tumour in a paper by Blair-Bell and Datnow.[39]

Wolfe and Kaminester[40] consider the folliculoid type of granulosa-cell tumour as the most mature and differentiated variety. They consider the diffuse forms to be immature. Meyer[41] states that the cells of the folliculoid forms have the greatest resemblance to the normal granulosa cells. This may be so with the small round type of cell, but does not appear so in the case of folliculoid forms composed of large polyhedral cells.

There are four points of difference between the oöphoroma folliculare and the folliculoid type of granulosa-cell tumour: (1) The cells of the oöphoroma folliculare are large pale cells resembling those of the primordial follicle; those of the folliculoid type of granulosa-cell tumour may be of the small round or oval variety, or may be the large deeply staining cells of the late granulosa about to be luteinized. (2) In the

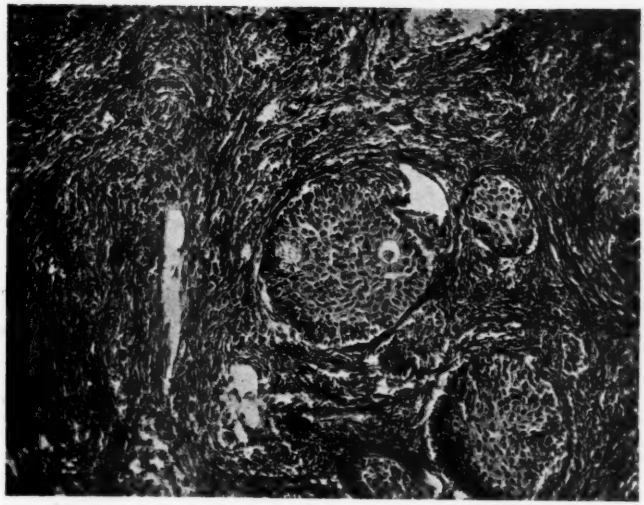

FIG. 1. (× 200)

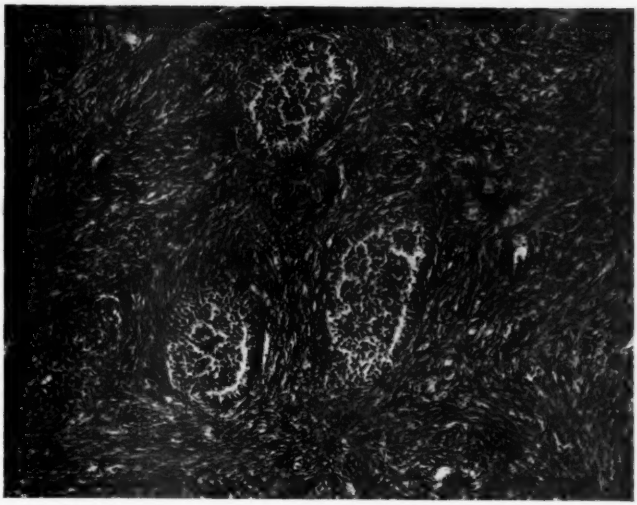

FIG. 2. (× 200)

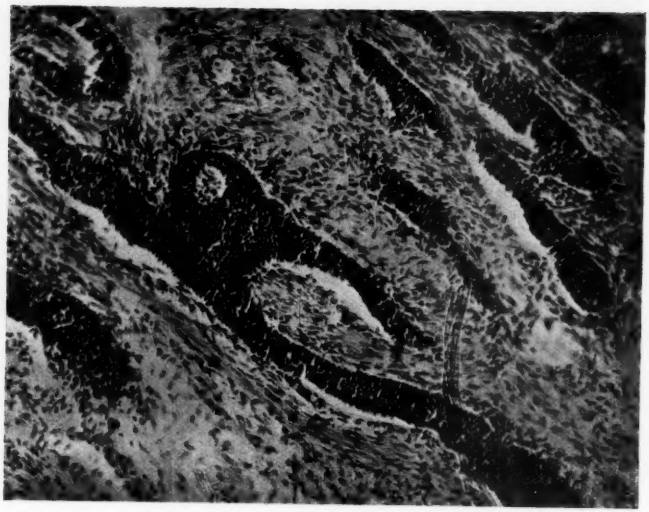

FIG. 3. (× 200)

Brenner tumour, the cells in the islets between the ova-like areas are solidly packed together; in the folliculoid granulosa-cell tumour the cells between the rosettes are very loosely packed and scanty, and the rosettes themselves do not bear so strong a resemblance to ova as do the corresponding areas of the oöphoroma folliculare. (3) Areas of cylindroid and diffuse types of growth are not found in association with the oöphoroma folliculare; such areas are commonly found in relation to the folliculoid granulosa-cell tumour. (4) Lastly, the occurrence of the oöphoroma folliculare appears to be confined to a later period of life than does the folliculoid granulosa-cell tumour, a point which will be dealt with later.

The Diffuse Type.

The diffuse or sarcomatoid type is the type most difficult to diagnose from a malignant ovarian neoplasm. It is practically impossible to recognize it as a granulosa-cell tumour unless some associated typical cylindroid or folliculoid area or transition form is sought and found in the tumour. Such association is common.

The diffuse granulosa-cell tumour is very cellular, and the blood-vessels are often primitive, the blood being separated from the tumour cells only by a single layer of endothelial cells. The cells show, however, the same uniformity in size and staining capacity as in the other two types of granulosa-cell tumour. This type of granulosa-cell tumour, as its name implies, is commonly confused with a small round-celled sarcoma of the ovary, from which it can only be distinguished microscopically by the uniformity of its cells, and the radial edge at the periphery of the growth. The cells of the small round-celled sarcoma are definitely variable in size, shape, and staining capacity, and show irregular mitoses.

The literature of sarco-carcinoma of the ovary and of small alveolar carcinoma of the ovary probably includes several cases of granulosa-cell tumour. Von Werdt[18] points out the similarity of the diffuse type of growth to sarcoma, and Robert Meyer[41] states that the change from the diffuse type to sarcoma may be observed in a tumour.

Transition Forms.

Transition forms between the folliculoid type and the diffuse type of granulosa-cell tumour are common.

In some areas of tumours, which would otherwise cor-

respond to the diffuse type of granulosa-cell tumour, spaces resembling Call-Exner bodies are found, with the cells radially arranged around them, as in the folliculoid type of granulosa-cell tumour. In some cases, this appearance is found only occasionally in isolated parts of the tumour, but in other tumours there is a generalized rosette-like arrangement of cells resembling that in the folliculoid tumours. The difference is that they are not arranged in small islets, but occur diffusely throughout the tumour. Such a case might well be described as a diffusely folliculoid growth. As in the diffuse form, the transitional form cannot be diagnosed as a granulosa-cell tumour unless a typical cylindroid or folliculoid area is found.

The Cylindroid Type.

The cylindroid or trabecular type of granulosa-cell tumour is a very characteristic growth-form, and commonly occurs in association with the other two forms. It is also sometimes termed a cylindromatous granulosa-cell tumour, or is simply referred to as a cylindroma.

This type of tumour exhibits strands of epithelioid cells in a connective tissue stroma. It is often described as a tumour in which the epithelial areas are cut up by ingrowth of connective tissue. Bizarre patterns may be formed by anastomosis of these strands. The cells in the epithelioid columns may be either one of the two cell-types found in the granulosa-cell tumours. Typically they present a radial edge to the surrounding connective tissue. There is not any appearance of invasion of the stroma by the epithelioid cells. When this type of growth occurs in association with the folliculoid or diffuse type, it is frequently found at the periphery of the tumour. Fig. 3 shows the appearance of a cylindroid growth composed of small round or oval cells. There are not any mitoses. Areas of diffuse growth are found in other parts of this tumour. The stroma is compact and condensed round the cellular strands, giving a theca-like appearance.

The specimen was obtained from an ovarian tumour removed from a woman of 48 by Miss M. Rawlins at the Elizabeth Garrett Anderson Hospital (Case 1, Lepper, Baker and Vaux[21]). The patient had had amenorrhoea for several months, following irregular menstruation for some months. One day before admission the patient had had acute lower abdominal pain, and was operated upon as an emergency. Torsion of the pedicle of a left ovarian tumour was found. The tumour was freely

movable, and there was free blood-stained fluid and blood-clot in the abdominal cavity. Only left salpingo-oöphorectomy was performed, since the condition of the patient did not warrant further operative measures. The tumour completely replaced the ovary. The greatest diameters were 10 inches by 6 inches. It had a firm fibrous capsule. On section, it was found to be partly cystic, partly solid. The cysts were filled with blood-stained fluid, and there was haemorrhage into the substance of the tumour at one pole. The colour of the tumour was pinkish-yellow and it was elastic in consistence. Microscopically, the cysts were lined with many layers of granulosa cells. The patient remains well nine years after the operation, without any evidence of recurrence.

Cysts.

The smaller cysts are lined by many layers of granulosa cells and resemble follicular retention cysts. The cells in the small cysts are in direct contact with the fluid inside them. In the larger cysts, lined with very large numbers of granulosa cells, the cells may be in contact with the fluid within the cyst, or, as Te Linde[19, 20] showed, there may be an inner zone of hyalinized fibrous tissue of variable width, separating the cells from the fluid.

Malignant Granulosa-cell Tumours.

The appearance of spaces containing acidophil fluid among the tumour cells, as occurs in the folliculoid type of tumour, and in the transition forms, is not by any means diagnostic of a granulosa-cell tumour. Such appearances are closely resembled by some cellular primary or secondary malignant ovarian neoplasms. In these tumours these appearances are evidence of degenerative changes and the cells around them are not arranged radially in a rosette-like pattern. The cells composing the tumour are entirely different from those of the granulosa-cell tumour in that they lack uniformity in size and staining capacity, are larger, and usually show active cell division. The stroma in malignant ovarian tumours is, as a rule, far less dense than in the granulosa-cell tumour, but theca formation around neoplastic cells is said to sometimes occur, even in malignant growths. This folliculoid appearance may be markedly seen in some cases of papillary carcinoma of the ovary.

It is doubtless the case that some tumours described as malignant cylindroid granulosa-cell tumours are in reality

secondary malignant neoplasms of other types. The cylindroid granulosa-cell tumour is very closely resembled by some cases of carcinoma of the ovary secondary to carcinoma of the stomach. It would be quite possible to diagnose such a case as a malignant cylindroid granulosa-cell tumour if the sections of the ovary only were available, if a clinical history was not given, and if the primary tumour, usually from stomach or breast, was not found. However, the cylindroid areas in the ovary present a definite contrast to those of the cylindroid granulosa-cell tumour. The cells in this secondary malignant neoplasm are of the same large irregular type as those in the primary tumour in the mucous membrane of the stomach. There is not any radial edge to the epithelioid areas, which are not sharply demarcated from the stroma, and which show definite invasion in several places. The stroma itself is much looser than in granulosa-cell tumours.

The histological appearances have been the cause of many granulosa-cell tumours being diagnosed as malignant growths, but when the cases have been followed up such opinions have not been borne out by clinical facts. That this error has been frequently committed is merely added confirmation of the fact that the histological appearances of these tumours are unusually difficult to evaluate. It is, however, quite obvious that many of the tumours described as malignant granulosa-cell tumours are indeed malignant. The question to be answered is whether they are granulosa-cell tumours or not. The necessity of a careful search for a primary tumour in cases in which a post-mortem is made may be stressed here. Cases of minute primary tumour with large ovarian metastases are likely to cause difficulty. Primary ovarian tumours which may resemble granulosa-cell growths are the malignant papillomata, sarcomata, endotheliomata and peritheliomata of the ovary. The literature of the last two types of tumour doubtless includes a few cases of granulosa-cell tumour, some cylindroid forms bearing a resemblance to these growths. Sarcomata are very rare. Briggs and Walker[42] found only one in 488 cases of solid ovarian tumours. The tumours in this case were bilateral, and the patient died soon after operation.

The recognition of malignant granulosa-cell tumours may eventually depend upon the possibility of the production of the hormone oestrin by malignant tumour cells. This is, however, unlikely, because malignant growths do not, as a rule, elaborate hormones. This point will be discussed later.

Schiller[24] and Te Linde[19, 20] stress the unreliability of hisology alone in assessing the malignancy of granulosa-cell tumours. Schiller's[24] 24 cases of granulosa-cell tumour include 16 non-malignant growths, six malignant growths, and two mixed or indefinite growths. The malignant growths are certainly such, on histological and clinical evidence. His benign cases are reported with after-histories, the length of which prove the non-malignancy of the tumours.

Malignancy is still a clinical condition, as it was of necessity in the days before histology came to the clinician's aid. There is thus, strictly speaking, no such condition as a " histologically malignant" tumour, a term to which Schiller[24] strongly objects. When histological opinion in these matters is not borne out by clinical facts, it is the histological diagnosis which must be revised in the light of later knowledge, and the limitations of the histological method must be recognized, in order that the widening of its sphere of usefulness may be increased by further research.

The diagnosis of granulosa-cell tumour should, therefore, be made with caution, and only (1) when several sections of different parts of the tumour, preferably large sections (e.g., 4 inches by 3 inches in size) are available, some of which show typical areas; (2) when the full clinical history supports the diagnosis; (3) when the gross specimen is available for examination; and (4) when the possibility that the ovarian tumour is a secondary growth has been excluded.

The Uterus.

The uterus in cases of granulosa-cell tumour shows characteristic changes which have excited much interest. At whatever period of life the tumour occurs, whether in childhood, during active sexual life, or after the menopause, the uterus is, as a rule, described as being enlarged to about the size of a 2 months' pregnancy. This fact has been mentioned in practically every report of granulosa-cell tumour, and has been particularly discussed by Arnold, Koerner and Mathias[43] in a paper on the endometrium in cases of granulosa-cell tumour. In cases in which the uterus has been removed, the endometrium is found, almost without exception, to be thickened and polypoid. Curettage likewise reveals an abundant endometrium. These changes are especially striking when occurring before puberty and after the menopause.

On section of the uterus, if this is removed, or on examination of the curettings, it is found that the glands are dilated and show

cystic changes. The condition may attain that known as Swiss-cheese hyperplasia, usually associated with non-ovular menstruation and the presence of a follicular cyst. The endometrium only rarely shows the premenstrual pattern.

Fahmy[44] considered granulosa-cell tumours as malignant neoplasms and stated that 3 examples, each of which was associated with hyperplasia of the endometrium, were included in his analysis of 937 cases of post-menopausal haemorrhage.

In Te Linde's[19, 25, 20] Case 4, the endometrium showed carcinomatous areas. He suggests that the vaginal bleeding of the last 3 months were probably due to the carcinoma of the uterus, but that the bleeding of the previous 3 years was due to hyperplasia of the endometrium accompanying the ovarian tumour—an oöphoroma folliculare. The patient was 62 years of age, and complained that her menses had never ceased. She had, however, had a period of 6 months' amenorrhoea 8 years previously, and since then had bled irregularly about once a month; the interval was often less than 30 days. During the last 3 months she had bled continuously. Previous to the 6 months' amenorrhoea her periods had been regular. Te Linde raises the question whether the uterine carcinoma might have been due to the constant stimulation of the endometrium by oestrin in a woman of this age.

The occurrence of adenomyosis of the uterus and of endometriosis with granulosa-cell tumour has also been described by Kleine,[45] Klaften,[46] and King,[47] the last-named author suggesting that the association of endometrioma with granulosa-cell tumour is important in suggesting a hormonal cause for the endometrioma formation. Klaften[46] also describes myoma of the uterus in association with granulosa-cell tumour. There is not any constant association of these conditions with this tumour, and their presence is probably fortuitous. It is, however, probable that the presence of a granulosa-cell tumour, because of its formation of oestrin, prevents the normal involution of uterine fibroids after the menopause.

Aetiology.

The Relation of Ovarian Histogenesis of the Granulosa-cell Tumour.

The genesis of the granulosa-cell tumour of the ovary is largely a matter of conjecture. The problem is intimately linked with that of ovarian embryology, about which, as yet, so little is definitely known that one finds the literature on the subject beset

with many and plausible hypotheses, but illuminated by few facts.

It is possible that the origin of the granulosa-cell tumour and of other ovarian tumours will have to be sought at an early stage in the development of the ovary. An aberrant localization of any wandering germinal cells might be the site of tumour formation at some later date in the life of the individual.

Fischel[48] is of the opinion that the granulosa is derived from the mesenchyme nucleus of the ovary, and that the germinal epithelium has nothing whatever to do with its formation. He considers, moreover, that the germinal epithelium does not form any part of the ovary—ova, connective tissue, or follicle cells—and that throughout life it exists merely as the peritoneal covering of the ovary. The production of follicle cells around the ovum from the ovarian mesenchyme is held by Fischel[48] to be due to a formative impulse from the ovum. The ovarian mesenchyme can thus form epithelial or connective tissue structures—the follicle cells and the stroma of the ovary.

Goodall,[49] on the other hand, states that all epithelial structures in the ovary are derived from the germinal epithelium and, further, that some of the interstitial cells are derived from the germinal epithelium, and some from the connective tissue of the Wolffian body. He believes that, in the human the formation of ova takes place exclusively during foetal life and the first two years of post-natal life, but that in lower mammals ovogenesis may go on throughout sexual life. The invasion of the cortical zone by germinal epithelium in post-natal or adult life which occurs in some mammals does not produce any ova, but Goodall[49] states that the invading epithelium is frequently the site of origin of neoplasms. An epithelial invasion of this sort might well give rise to a granulosa-cell tumour, the follicle cells, which are the precursors of the granulosa cells, being derivatives of the germinal epithelium. Against this possibility is the fact that such an invasion has not been observed in the human being. Goodall,[49] however, supposes that if the germinal epithelium in the human female should become invaginated for any reason, it would be liable to the formation of neoplasm.

Allen,[50] in 1923, found that in the mouse ovogenesis occurred throughout adult life.

Evans and Swezy,[51] in 1931, showed that in the rat, guinea-pig, dog, and cat, ovogenesis occurs throughout adult sexual life. They further state that this is also the case in the monkey and in man. According to this hypothesis, there is a rhythm of

production of ova from the germinal epithelium, and their subsequent destruction, which Evans and Swezy[51] call the "follicular cycle". This production-destruction rhythm is related to the ovulation cycle, and not necessarily to the menstrual cycle. The proliferations of germinal epithelium give rise to ova and follicle cells. The destructive phase of the cycle usually begins by degeneration of the granulosa-cells, though sometimes the first signs of degeneration are in the ovum. The rhythm of the follicular cycle is not obliterated during pregnancy. According to this view of ovogenesis, the life of the ovum is very short, and, apart from the elements of the blood, it probably has the shortest life-span of any cells in the body. This is an opinion opposed to the usual belief that the ova necessary for the whole life of an individual are formed before birth, and that many of them, as estimated by Waldeyer, must live as long as 50 years or more.

A constantly recurring production and destruction of ova and follicle-cells from the germinal epithelium would account for a much greater possibility of tumour formation from follicle-cells than is now supposed to be the case. Evans and Swezy[51] state that, although the destructive phase of a cycle usually begins by degeneration of follicle, or granulosa-cells, the first degenerative changes may occur in the ovum. If, in any case, the ovum should degenerate, and the follicle-cells attached to it should still be healthy when a new productive phase overtook the ovary, it is very reasonable to suppose that the follicle-cells thus left ovumless would be acted upon by the growth impulses, and that they might exhibit marked growth changes, or actually tumour formation. Such a tumour would be a granulosa-cell tumour of the ovary.

Robert Meyer,[52] in attempting to explain the origin of granulosa-cell tumours of the ovary, has drawn attention to granulosa-cell rests which he has frequently found in the medullary part of the ovaries of foetûs at term and also in those of newly born children. These rests of granulosa-cells are ovumless, and, according to Meyer,[52] may persist throughout adult life in an undifferentiated state, and at any time of life would be capable of producing granulosa-cell tumours. Meyer[52] states that such masses of embryonic cells can persist into the menopause, when normal follicular cells have disappeared, and he thus explains the origin of granulosa-cell tumours in menopausal patients. He stresses the dependence of the normal follicular epithelium upon the ovum during the whole of its existence, from follicle-cell to corpus luteum, and believes that

the adult, differentiated follicle-cell is incapable of tumour formation, and that we must, therefore, look to embryonic cells as the source of such growths. In normal circumstances, the only type of granulosa which can outlive the ovum is luteinized granulosa, or the granulosa of follicular cysts, which is thought to be short-lived.

Walthard[53] described circumscribed cellular areas in the ovarian cortex, most of which he found in the ovaries of foetûs and newly born children. He considered that these were capable of forming ovarian tumours. They are sometimes considered to be possible sources of origin of granulosa-cell tumours, but many authors agree that the cells of Walthard's cell complexes do not resemble granulosa cells. Robert Meyer[26] considers that the oöphoroma folliculare, or Brenner's tumour, may arise from cells of Walthard's areas in the cortex.

Blair-Bell[54] includes the granulosa-cell tumour as an ovarian neoplasm of intrinsic origin, and one of the lepidomata. The general opinion is that the main sources of lepidic neoplasms of the ovary are the capsular epithelium, the Wolffian epithelium, and cells of the granulosa.

Schiller[24] upholds Fischel's view[48] of the genesis of the follicle-cells and of the ovarian stroma from the mesenchyme of the ovary. He considers that this theory is the one which best explains the various microscopic appearances found in granulosa-cell tumours. The dual potentialities of the mesenchyme would enable embryonic rests of mesenchyme to produce a tumour consisting mainly or solely of epithelial elements, one composed mainly of connective tissue elements, or any intermediate combination of epithelium and connective tissue, which appearances are found in different granulosa-cell tumours. The hypothesis is, then, able to explain the facts in an adequate way.

Szathmáry[55] attributes the different histological appearances to the manifold capacity for growth of the granulosa, and to the active or passive behaviour of the connective tissue.

Meyer's[52] hypothesis of origin of the granulosa-cell tumours from undifferentiated embryonic rests of granulosa tissue is the one most commonly accepted. The fact that early granulosa-cell tumours, such as the one described by Te Linde,[19, 25, 20] which was only 3 mm. in diameter, are found in the medulla of the ovary, suggests that the origin of such tumours cannot be from ripe follicle-cells which are present in the ovarian cortex, and may be from embryonic rests of granulosa cells. These rests are described by Meyer[52] as being medullary in situation.

Robert Meyer's hypothesis[52] stresses the improbability of tumour formation from adult follicle-cells, rather than proves the origin of the tumours to be from embryonic granulsa-cell rests.

The age-incidence and age-liability of 200 published cases, as will be shown, are greatest during the 40 to 50 and 50 to 60-year age groups. The incidence before puberty and after the menopause is also probably greater than in other ovarian tumours, as, for example, the pseudomucinous cystadenoma of the ovary. It seems very probable, therefore, that the granulosa-cell tumour may prove to be the expression of irregular or unbalanced ovarian activity, which would be most likely to be found in the years nearest to the menopause, i.e., the years of greatest liability to this tumour. In cases which occur before puberty, the ovary, normally inactive at this time, may, in such cases, have been the site of premature activity. Such being abnormal at this age, a granulosa-cell tumour may be the result of unrestrained and unbalanced ovarian activity. In these cases there is, therefore, a question whether the granulosa-cell tumour is the cause of precocious puberty, or *vice versa*. When sexual activity has normally ceased, it is well known that a final exacerbation of ovarian activity may occur, being evidenced by the rare cases of pregnancy occurring a year or two after an apparently normal menopause, or by a final menstrual period which occurs within a year or two of the menopause. It is very likely that a further and more common expression of such abnormally late activity may be the production of a granulosa-cell tumour. Some patients are found to have had irregular periods since puberty. This is very suggestive of irregular ovarian activity having occurred over many years in these patients.

Lastly, mention should be made of attempts experimentally to produce granulosa-cell tumours in mice. By careful regulation of X-ray dosage, it has been found possible to destroy the ova and to leave the follicular epithelium intact, or so slightly damaged that it soon recovers its normal vitality. The granulosa would thus appear not to be so intimately dependent on the ovum, as Meyer[52] and others have suggested. Schiller[24] found it impossible to produce a granulosa-cell tumour by injections of pregnancy-urine or of anterior pituitary extract into mice the ovaries of which had been radiated as described. The pregnancy-urine and anterior pituitary extracts were given in prolonged courses. When, however, an alcoholic tar extract was given concomitantly with the anterior pituitary extract, a tumour was produced in

the ovary of one of the mice which, according to the author, was a typical granulosa-cell tumour. At the time of publication of Schiller's book,[24] the work was being continued, and further reports have not yet been received.

The natural occurrence of ovarian tumours in mice is extremely rare. However, an interesting case has been reported by W. U. Gardner, L. C. Strong, and G. M. Smith,[56] of a mouse in which they found the following abnormalities at autopsy: (1) pituitary adenoma; (2) multiple mammary adenocarcinomata and generalized cystic hyperplasia of the mammary gland; (3) bilateral granulosa-cell tumours of the ovary; and (4) hyperplasia of the endometrium of the uterus. They could not attribute any definite physiological activity to the pituitary adenoma, and do not suggest that it was the cause of the ovarian condition. The uterine condition, and the generalized cystic change in the mammae they attribute to the granulosa-cell tumours. Metastases were not found at the autopsy. A point of great interest is that the mouse was apparently sterile. It was 695 days old and had given birth to the last of its four litters 371 days previously. It had since been in breeding cages in contact with males, i.e. for more than a year, but had not had any further pregnancies. This finding is in support of the opinion that granulosa-cell tumours may cause sterility in the human.

Whether the origin of the follicular epithelium is from the germinal epithelium or from the ovarian mesenchyme, is still a matter of dispute, as is also the alleged existence of embryonic granulosa-cell rests, but it is generally accepted that the tumours in question are derived from the follicular epithelium in different stages of its development. The origin of the follicular epithelium itself is still unknown. The endocrine action of the tumour further supports the view that it is derived from the granulosa which normally elaborates oestrin.

Endocrine Action of the Granulosa-cell Tumour

The importance of the endocrine action of the granulosa-cell tumour is being realized more and more. That it is this activity which causes the characteristic symptoms has already been mentioned, and the few cases in which examinations for this function have been made may now be discussed. The tumour-cells are derivatives of the follicle-cells which are normally associated with the production of oestrin. The production of oestrin usually occurs in excess when excessive amounts of follicular epithelium are present, as in the follicular cyst of the ovary.

Production of excess of oestrin by granulosa-cell tumours, as evidenced by finding excess of oestrin in blood or urine, has not yet been proved. It is probable that it will eventually be found, and it is meanwhile very necessary to collect information on this point wherever possible.

The attempts which have already been made to prove the presence of oestrin in the blood and urine of patients with granulosa-cell tumour, when this has been diagnosed before operation, have been few. Schuschania[57] reported that in a patient of his, aged 67 years, there was quantitative excess of oestrin in blood and urine before operation for removal of a granulosa-cell tumour. The excess disappeared after operation. This case is usually cited as one which shows beyond all doubt that the tumour concerned produced oestrin, but the figures given by Schuschania[57] are not entirely conclusive. He concentrated the urine collected for 5 days before operation and found in the extract of the total amount only 326 mouse-units of oestrin. In the total faeces over a similar period he found 619 mouse-units. Thousands of mouse-units would be expected on analogy with the amounts found during pregnancy, and the fact that the other ovary was cystic is a further point which lays the conclusions open to doubt. If this cyst were a follicular cyst (a point not made clear by Schuschania[57]) it alone would be able to give rise to the amount of oestrin found. Tumour-implants into castrated mice gave negative results; extracts of the white area of the tumour were negative, but extract of the infarcted area yielded 4 mouse units of oestrin. A Frank test performed on blood from a vein, taken on the day of operation, was positive, as it was on blood taken from a vessel in the tumour's capsule. Prolan A was found in the urine before operation; prolan B was not found.

Eight days after the operation, at which total hysterectomy and bilateral oöphorectomy were performed, the urine contained 158 mouse-units of oestrin, and 66 to 70 days after the operation a 5-day's total of urine and faeces did not yield any oestrin. Schuschania[57] described this case as a malignant granulosa-cell tumour, though the tumour was unilateral, freely movable, and showed no metastases. The uterine mucous membrane was hyperplastic. Interesting as the experiments are, they do not prove the production of oestrin by a granulosa-cell tumour.

Meyer[58] obtained a positive oestrous reaction in spayed mice by injection of tissue from a granulosa-cell tumour from a woman of 36 years.

Frank obtained evidence of the presence of oestrous hormone

in material obtained from the ovarian tumour of a child of 3 years and 11 months (Eastlake's case[79]). He tested the tumour material on the mouse and rat, and reported "some activity which shows that the tumour elaborated the female sex hormone."

Neumann[59] found oestrin present in 40 c.c. and in 20 c.c. of blood removed before operation in a case of granulosa-cell tumour in a woman aged 46 years. In this case, oestrin was not found in 80 c.c. of blood removed six weeks after the operation. Also, in a case aged 61 years, he found oestrin present in 60 c.c. of blood removed pre-operatively, and a piece of the tumour and some tumour extract gave a positive oestrous reaction in spayed mice. In this case oestrin was not found in 60 c.c. of blood removed 18 weeks after the operation.

Thornton[60] describes a patient aged 53 years, in whom the menopause had occurred six years previously, and who had been bleeding from the uterus for a year. A folliculoid and cylindroid granulosa-cell tumour was removed. The urine was collected over 31 hours, beginning 24 hours after the operation. A total amount of 1,045 c.c. was collected. Of this 10 c.c. were used for a Friedman test, which was negative for prolan A and B, and the remainder was concentrated by boiling and then extracted with ether. The ether was evaporated and the residue taken up in 20 c.c. water, and was injected into 3 spayed mice, previously shown not to be having oestrous cycles.

The first mouse received 10 c.c. of extract given in 4 injections of 2.5 c.c. each over 24 hours. A positive oestrous reaction was found 24 hours after the first injection. The second mouse received 5 c.c. of extract given in 2 injections of 2.5 c.c. separated by 10 hours, and did not show any oestrous reaction. The third mouse, receiving 3 c.c. in 3 injections of 1 c.c. each over 15 hours, came into oestrus 24 hours after the first injection. Thornton[60] does not explain the inconsistency of these results. The second mouse may have been less sensitive to oestrin than the third. This experiment shows definite evidence of the presence of oestrin, which is most likely to be due to the granulosa-cell tumour.

In the case of a granulosa-cell tumour in a child of 7 years, described by Bland and Goldstein,[61, 62, 63] the oestrin test was positive 2 days before operation, and the Zondek-Aschheim test was negative. Seven days after the operation, oestrin was found to be absent. When this tumour recurred two and a half years later, oestrin was found in blood and urine pre-operatively, and

the Zondek-Aschheim test was also stated to be positive. The latter finding is most unexpected and is unexplained. Both tests were negative 14 days after the operation. There is also no explanation for the case described by Pahl,[64] in which, 9 days after operation for removal of a granulosa-cell tumour in a girl of 9 years, a positive Zondek-Aschheim reaction III was found. Later tests in this patient were always negative.

If the granulosa-cell tumour produces a large amount of oestrin, this is probably eliminated from the body within a few days after removal of the tumour, as occurs after labour. Tests for oestrin should thus be performed within 48 hours of removal of the tumour, if the diagnosis is not made until operation, if any hope of positive results is to be entertained. It is much preferable to test the pre-operative urine when this is possible. Schulze[65] described the case of a patient of 46 years in which a test for oestrin was performed 1 month after removal of a granulosa-cell tumour. It was not unnaturally found to be negative.

Schulze[65] considers that examination for large amounts of oestrin in the urine in cases of suspected granulosa-cell tumour will become as important for diagnostic purposes as is the Zondek-Aschheim reaction for cases of suspected hydatidiform mole and chorion-epithelioma. Such examinations may make the pre-operative diagnosis of the granulosa-cell tumour much more possible than at present. The endometrial changes associated with granulosa-cell tumour are found to be characteristic of those found after prolonged action of the oestrous hormone. These changes are similar to those which Parkes[66] was able to produce in the endometrium of spayed mice by giving large doses of oestrin.

Several authors have described the presence of prolan A in the urine of patients with granulosa-cell tumours. This finding has also been reported in the case of other ovarian tumours, and its significance is not fully understood. It is only significant at all if found before the menopause, since the presence of large amounts of prolan A in the blood and urine normally after the menopause obscures any excess associated with a granulosa-cell tumour. Such a finding is described by Dworzak and Podleschka[67] in a woman of 50 years of age, but the clinical details do not show if she was menopausal or not. In this connexion, Kleine's case,[45] in which the pituitary body was examined in a woman of 61 years of age, who came to autopsy 2 days after removal of a granulosa-cell tumour, is interesting. The pituitary did not show any detectable changes.

The possibility of the granulosa-cell tumour being caused by hormonal action of the pituitary is unlikely, since excess of hormone can give rise to hyperplasia in an organ dependent upon it, but not to neoplastic formation. An example of such hyperplasia due to the hormone's action is afforded by the endometrium in cases of granulosa-cell tumour. The cystic hyperplasia found in these cases is probably due to excess of oestrin. Definite recognition of malignant granulosa-cell tumours may depend upon their capability of producing oestrin.

The possibility that malignant tumours of endocrine glands may be able to elaborate hormones which are the same as those formed by the normal gland is suggested by Eiselsberg's[68] case of thyroid carcinoma. In this case, a patient suffering from hyperthyroidism was found to have a carcinoma of the thyroid gland. After removal of the growth, hypothyroidism supervened. This gave place to a normal condition and finally to hyperthyroidism again, as the metastases of the growth appeared. It is even possible that Eiselsberg's explanation[69] of this thyroid tumour being the site of formation of hormone may be entirely wrong. The symptoms in the first place may have been due to coincident hyperplasia of normal thyroid tissue as a reaction to the presence of the growth. After the malignant thyroid gland was removed, presumably completely, the hypothyroidism which came on was possibly due to removal of normal glandular tissue with the malignant tissue. The metastases, which were accompanied first by return to normal and later by progress to hyperthyroidism, may have stimulated some normal aberrant thyroid tissue which was not known to be present, to excessive function. It is thus obvious that no proof is deducible from this case that a malignant endocrine tumour can produce an increased amount of normal hormone.

The rarity of such a finding makes it unlikely that granulosa-cell tumours will be found to differ from other malignant tumours of endocrine glands, and we may, therefore, have extreme difficulty in finally separating them from other growths which resemble them.

The symptomatology of the granulosa-cell tumour at all periods of life can be explained on the basis of action of excess of oestrin. The amenorrhoea occurring during active sexual life has been suggested by Novak[23] to be due to progestin formed by the tumours, but could be as well explained by the action of oestrin alone, as is the amenorrhoea found in association with follicular cysts of the ovary, which is thought to be due to

a persistently and constantly high level of blood-oestrin. Normal menstruation is accompanied by fall in the level of blood-oestrin which (according to Zondek[69]) is at its height on the nineteenth to the twenty-first day of the menstrual cycle. Allen,[70] working with monkeys, has shown experimentally that constant excess of oestrin in the blood does not give rise to uterine bleeding, but to cystic hyperplasia of the endometrium, and that only when the oestrin is withdrawn does uterine bleeding supervene within a day or two. The cases of granulosa-cell tumour in which amenorrhoea is found might thus be explained by the level of blood-oestrin being constantly raised. When uterine haemorrhage supervenes, or when irregular haemorrhages form the sole evidence of menstrual disturbances, this might be due to some factor which causes the level of blood-oestrin to fall or to fluctuate. Schubert[71] suggests that after a particular threshold value is reached, in the normal menstrual cycle, some central regulatory mechanism causes a rapid fall in hormone production, and only after an interval of time can the cyclic formation of hormone begin again. Such a central regulatory mechanism may be postulated for the cases of granulosa-cell tumour in which uterine bleeding is a feature. It is strange, however, if a central regulatory mechanism is active, that some patients can have long periods of amenorrhoea presumably due to constantly high blood-oestrin, before uterine bleeding begins. The suggestion may be made that the supervention of uterine bleeding in such cases is not due to a central regulation of hormone production, but to some intrinsic change in the tumour which causes its production of hormone to fall or to become irregular. Jeffcoate[72] suggests that there may be a bleeding factor elaborated by the anterior pituitary gland, which is released by withdrawal of oestrin and progestin, and which causes uterine bleeding The bright yellow colour of some of these tumours certainly suggests that change to early lutein tissue may have taken place, but even if this has occurred, the tumour tissue will probably still produce oestrin, for Allen[70] states that progestin has not yet been found in the human corpus luteum, but that large quantities of oestrin are found. Reports are not yet available of examination for progestin in the tumour substance, or in blood and urine of cases of granulosa-cell tumour.

The rare occurrence of virilism in cases of granulosa-cell tumour is entirely unexplained. The most likely possibility is that the granulosa-cell tumours in such cases are wrongly diagnosed as such, and that arrhenoblastoma of the ovary (a

non-malignant ovarian tumour originating from embryonic rests in the ovary which have male potentialities) has been mistaken for a granulosa-cell tumour.

Clinical Characteristics.

Incidence Compared with that of Other Ovarian Tumours.

Granulosa-cell tumours of the ovary are comparatively rare, but their true incidence is difficult to assess, since it is obvious that many mistakes in diagnosis have been made, a point which has been discussed in the section on histology. Thus, the records at present available suffer from such inaccuracies.

The cases which I have collected from the literature number about 200. In collecting these cases, all those which have been discussed as granulosa-cell tumours by their own authors have been included, as it is obviously impossible, when working with the *data* from published records, to assess each separate case accurately. The records are, generally speaking, not sufficiently well illustrated to enable an accurate criticism to be made of the histology, and though the clinical histories show a consistently high standard, the after-histories are, on the whole, very scanty. The largest number of cases previously collected from the literature was 150, collected by Plate[73] in 1932. Bland and Goldstein[63] have recently collected 160 granulosa-cell tumours and 66 Brenner tumours, and state that 85 further cases of granulosa-cell tumours are reported in groups by various authors. They separate the granulosa-cell tumour and the Brenner tumour (the oöphoroma folliculare) as being two entirely different growths. In the cases I have collected, these tumours are both included wherever their authors have so included them. There are thus many cases of Brenner tumour reported separately which have not been included here, such as those in the series reported by Meyer.[26]

Szathmáry,[74] reviewing 1,114 ovarian tumours of all types treated surgically at the II Gynaecological Clinic at Budapest, described 9 granulosa-cell tumours, i.e. 0.9 per cent, which he included among the solid carcinomata of the ovary. Klaften,[46] in a series of 247 ovarian tumours, found 10 granulosa-cell tumours, i.e. 4.04 per cent, which he also included among the carcinomata. Fauvet,[75] who examined 367 ovarian tumours removed at the Leipzig Gynaecological Clinic in 4 years found 5 granulosa-cell tumours, or 1.4 per cent. He, too, classified them among the carcinomata.

It is thus evident that these tumours are relatively rare, but

their occurrence at all periods of life, their endocrine influence, which is most striking before puberty and after the menopause, and their clinical non-malignancy render them very worthy of investigation.

Age Incidence.

Granulosa-cell tumours are found to occur at all periods of life. Schiller[24] states that they occur generally in post-menopausal life. Novak,[23] in examining 38 cases, shows that, in that series, the greatest incidence is between the ages of 40 and 50 years and that more cases occur from 0 to 10 years than from 10 to 20 years. Bland and Goldstein,[63] in their recent paper, tabulate 150 cases in 10-year age groups, and find that the incidence of the granulosa-cell tumour gradually rises from puberty until the 50 to 60 age group, when it is at its maximum, after which its incidence declines. They find that the Brenner tumour, on the other hand, has a maximal incidence from 60 to 70 years, and is not found at all before the age of 20 in the 66 cases enumerated by these two authors. They also find the incidence of granulosa-cell tumours between 0 and 10 years to be greater than their incidence between 10 and 20 years. Meyer[41] states that the granulosa-cell tumour occurs most frequently in women from 60 to 74 years of age, but his published cases do not bear out this point any more than do the other cases in the literature.

The youngest case reported up to now is one of Kleine's[45] in which a unilateral granulosa-cell tumour was removed from a child of 3 years and 5 months. The patient showed typical precocious puberty with uterine bleeding, enlargement of the breasts, and growth of pubic hair. The symptoms retrogressed after removal of the tumour, and the child, when seen at the age of 12, 8 years and 6 months after the operation, was well and free from recurrence.

The oldest case yet described is one of Schiller's,[24] the patient being 76 years of age. The patient died soon after the operation, the cause of death being pulmonary embolism.

Klaften,[45] in reviewing 80 cases collected from the literature, publishes a Table which shows the same characteristics as regards age incidence as are found in an examination of the 200 cases I have collected.[76]

The incidence of granulosa-cell tumours in these 200 cases is shown to be much greater in middle life than during the first 25 years, and is maximal between the ages of 45 and 54 years. They are thus most common during the period of the meno-

pause, but are by no means confined to that time. Only 6 per cent occur after the age of 65 years.

The age-liability of these tumours is the incidence per 1,000 women alive in each age-group, and an age-liability curve can be constructed which shows that there is a marked falling off in liability as well as in case-incidence after the age of 60 years.[76] On the figures given, the relative liabilities at 50 and 70 years of age are as 3:1. The liability is least of all in old age, being less at 80 years than in childhood; it is found to rise slowly from the ages of 3 years and 6 months to 20 years, and rapidly from 20 to 50 years; it then falls slowly from 50 to 60 years and rapidly from 60 to 80 years. These figures cannot be regarded as entirely accurate, because only 200 cases are available for examination, and their reliability is further reduced by the fact that, since published figures are used, there will be a tendency for the more striking cases—namely, those before puberty —to be put on record, and for examples of the better known type, the case occurring in late middle-age, to be regarded as not worthy of publication.

A similar analysis has been made of 200 consecutive cases of pseudomucinous cystic adenoma of the ovary, selected from the records of St. Thomas's Hospital, London. The results cannot be compared with those for granulosa-cell tumours without qualification, owing to the different origins of the age-incidence *data* in the two cases, but the contrast between the two sets of figures is sufficiently striking to be of some significance. The proportion of granulosa-cell tumours occurring before the age of 14 years is 7.5 per cent; that of pseudomucinous cysts is 0 per cent. This is too large a discrepancy to attribute merely to misleading *data*, and it must be concluded that there is a genuine tendency for the granulosa-cell tumour, as contrasted with the pseudomucinous cyst, to occur before puberty. This does not mean that the granulosa-cell tumour is actually more common before puberty than is the pseudomucinous cyst. The reverse is quite possibly true. The statement means either that the granulosa-cell tumour shows a distinct preference, as compared with the pseudomucinous cyst, for the conditions which obtain before puberty, or that when some unusual factor induces a premature puberty a granulosa-cell tumour is particularly liable to develop, whereas a pseudomucinous cyst is not.

The pseudomucinous cyst is much more strictly confined to the child-bearing period, according to these figures, than is the granulosa-cell tumour.

Symptoms.

These will be discussed in relation to the three periods of the sexual life of woman, namely (1) before puberty; (2) during active adult life; and (3) after the menopause. The symptoms and signs dependent upon the mechanical effects of the presence of a pelvic tumour occur in all cases at all periods of life, unless the tumour is too small to produce such effects. The characteristic uterine changes which have been described are found at all ages.

(1) *Before puberty*. Eleven cases of granulosa-cell tumour occurring before puberty have been described. All these children showed precocious puberty. The cases may be enumerated as follows: Blau,[77] 1 case aged 5 years; Pahl,[64] 1 case aged 9 years; Rummeld,[78] 1 case (published also by Habbe[37]) aged 5 years; Bland and Goldstein,[61, 62, 63] 1 case aged 7 years; Eastlake,[79] 1 case (later again reported by Novak[80]), aged 3 years and 11 months; Novak,[80] 2 cases aged 5 and 6 years; Kleine,[45, 81] 1 case aged 3 years and 5 months; Klaften, 2 cases aged 4[82] and 9 years;[83] Best,[84] 1 case aged 6 years.

The age below which onset of puberty may be rightly termed precocious is frequently taken as 12 years. Wheelon,[85] however, states that the normal limits of puberty are from 10 to 16 years, and that the term precocious puberty should be confined to cases occurring below the age of 9 years. Precocious puberty is commoner in girls than in boys. It has been known to occur from ancient times, and was first described by Craterus,[86] the brother of Antigonus, and his writings indicated that it was known to the Ancients before him. It was discussed by Pliny the Elder.[87]

Krabbe,[88] in 1919, collected 150 cases of precocious puberty and about 30 have been described since then. It may occur in the first year, or even in the first month. Pregnancy has been described in association with precocious puberty, as in the cases of Mandeslo[89] and Haller.[90]. Mandeslo's case[89] (1658) was that of a child in whom menstruation began at the age of 3 years, and a son was born at the age of 6 years. In the case described by Haller[90] (1751), menstruation began when the child was 2 years of age, and a dead child was born at 9 years. This patient menstruated until the age of 52 years. Pregnancy with precocious puberty can only occur if ovulation takes place, and this probably does not occur when a granulosa-cell tumour is the cause of precocity.

In cases of precocious puberty due to the presence of a

granulosa-cell tumour, the first evidence of any abnormality is usually the occurrence of vaginal bleeding. The child grows rapidly, and usually becomes mentally, as well as physically, in advance of its age. The breasts become enlarged, as in normal puberty, and pubic and axillary hair appear. The vaginal bleeding is recurrent and may simulate precocious menstruation in its regularity, occurring for a few days every 28 days. In other cases, the bleeding may be irregular, and may be scanty at first, but increasing in amount until flooding occurs later.

The changes in the child resemble those at puberty, when the feminizing hormone exerts its action, and it is probably correct to assume that precocious puberty in association with granulosa-cell tumour is due to oestrin produced by that tumour. These symptoms retrogress after the removal of the tumour, and the child later undergoes the changes of puberty at the normal age.

Eastlake's case[79] is especially interesting because portions of the tumour were found by Frank to have oestrous activity. At the time of its removal, the tumour was reported to be an embryonal carcinoma of the ovary. The patient was well 2 years later, and the case was reported by Novak[80] as one of granulosa-cell tumour of the ovary.

Kleine's case,[45, 81] aged 3 years and 5 months, was found to be well 8 years and 6 months later, when last seen.

The case of Bland and Goldstein[61, 62, 63] ceased to menstruate after removal of the tumour, but menstruation began again 18 months after the operation. This recurred every month for 3 months. The child was examined, a pelvis mass was again found, and oestrin was found in the blood and urine. Radiological examination did not show any evidence of metastases in the lungs or mediastinum, in the skull, thoracic or lumbar vertebrae, in the pelvic bones, or in the bones of the extremities. A second granulosa-cell tumour, developing in the other ovary, was then removed, and was found to be exactly of the same nature as the first. The endometrium was mature and in the interval stage. The child was well 6 months after the second operation. Two days before the first operation on this child, oestrin was found in the urine, and radiological examination showed marked ripening or precocious development of the epiphyses at the lower end of the humerus, and at the upper end of the radius. Union of epiphyses with diaphyses had occurred, both at the upper and lower ends of the femur. This fusion is 7 to 10 years earlier than under normal conditions. The sella turcica seemed to be within normal limits, and the clinoid processes were well formed.

Rummeld's case[78] was one of a child of 5 years, who had menstrual bleeding and mammary hypertrophy. Bilateral granulosa-cell tumours were found; the left ovarian tumour was removed, and part of the right ovarian tumour, a portion of what was hoped to be normal ovarian tissue being left. The bleeding and enlargement of the breasts retrogressed, but returned 3 years later, when the tumour was found to have recurred. Operation for removal of the second tumour was followed by disappearance of the symptoms. The patient was later found to be well and free from further recurrence of a granulosa-cell tumour.

Blau's case[77] was well a year later, as was one of Novak's cases;[80] Pahl's case[64] recovered; Klaften's case, aged 4 years,[82] was well 6 months later, and his case, aged 9 years,[83] died from weakness a year later, after suffering from headaches, visual and auditory disturbances, and diminished mental capacity for 6 months. The after-history of Novak's[81] other case is unknown; and none is available for Best's case,[84] which was reported soon after the tumour had been removed.

With reference to the very early occurrence of precocious puberty, it is interesting to note a case of puberty occurring in a child of 1 year and 6 months, described by Polano[91] in 1923. This child had had uterine bleeding in October and December 1922, and in January 1923, on each occasion the bleeding lasting for two days. She also had a growth of pubic hair. At the operation in March 1923, a right-sided ovarian tumour was removed, the left ovary was reported to be normal, and the uterus 5 cm. long. The ovarian tumour was described as a myxosarcoma with follicle-like areas. It is possible that this diagnosis is incorrect and that this is the youngest case of granulosa-cell tumour yet described. Illustrations are not given in Polano's paper.[91] The child died 6 hours after the operation and autopsy findings were not recorded.

(2) *In active adult sexual life.* This is the most difficult period in which to make the diagnosis of granulosa-cell tumour of the ovary. After the menopause, uterine bleeding, and before puberty, precocious puberty, are arresting symptoms, which, when associated with the presence of an ovarian tumour, are very suggestive of its being a granulosa-cell tumour. During active sexual life, however, the symptoms are not nearly so easy to assess.

Disturbances of menstruation are the rule. Szathmáry[55] states that irregular bleeding is found in 85 per cent of patients at all

ages, and this is probably a low estimation of the facts. There may be a period of amenorrhoea, which, in cases of granulosa-cell tumour, often lasts for years, and is subsequently followed by uterine bleeding which is usually of an irregular and excessive character. The bleeding is the symptom which usually brings the patient to the gynaecologist. The period of amenorrhoea is occasionally broken by one or two small isolated uterine haemorrhages. In the patients of Lepper, Baker and Vaux,[21] amenorrhoea in this period of life was found in every case, and, unless torsion of the tumour occurred, it was followed by uterine bleeding. Wilfred Shaw,[92] writing in 1932, discussed 2 cases of granulosa-cell tumour in his wide review of ovarian tumours. He describes them with the ovarian carcinomata. One patient was 23 years of age, the other 30; 1 was married and sterile, the other single. Each patient had had amenorrhoea followed by severe uterine bleeding. The tumours were in each case unilateral. One patient was alive and well 4 years after panhysterectomy and radical removal of the tumour. The other patient died two months after operation, and at autopsy was found to have metastases in the pelvis, on the peritoneum, in the liver and stomach, and in the pleura.

The commonest type of menstrual disturbance reported in the literature is not amenorrhoea followed by bleeding, but irregular, frequent and excessive haemorrhage. The patient, becoming exsanguinated and weakened, consults a gynaecologist on account of the bleeding. This symptomatology may also be caused by a follicular cyst of the ovary, and may be presumed to be due to periodic drops in the high level of oestrin in the blood.

It has been shown that regular menstruation can occur without ovulation in the presence of a follicular cyst of the ovary. It is possible that there may be a similar occurrence of regular non-ovular menstruation in association with a granulosa-cell tumour. Such absence of menstrual disturbance is extremely rare, but when such disturbance is absent the symptoms of a growing pelvic tumour may be the first evidence of its presence.

Sterility may be a symptom of granulosa-cell tumour of the ovary. In few cases this is specially mentioned. Schulze[65] described the case of a woman of 27 years of age who had been married for 5 years, was sterile, and anxious to have children. Until 2 years previously her menses had been regular and very profuse. For the last two years they had been irregular and scanty, occurring every 1 to 2 months, and lasting only a day. The last menstruation was 3 months

before admission. Six months previously, a gynaecologist of repute had reported that the pelvis was normal. When admitted, a left-sided adnexal mass was found, which was thought to be an ectopic pregnancy on account of the amenorrhoea. At operation a left ovarian cyst was found, 5 cm. in diameter. Dilatation and curettage, left salpingo-oöphorectomy, removal of the appendix, and tonsillectomy were performed. The ovarian cyst was ruptured in removal. Its contents looked like infarcted placenta. On section, it was first diagnosed as medullary carcinoma of the ovary and was later found to be a folliculoid granulosa-cell tumour. The patient has remained well for 15 years after the operation, and has one child—a boy—born 2 years after the operation. An unusual feature of this case is the fact that the uterus was small, $2\frac{3}{4}$ inches by sound, and hardly any endometrium was removed by the curette.

A patient aged 27 years, reported by Wolfe and Kaminester,[40] had been married for 4 years and had never been pregnant.

It is possible that some unexplained cases of sterility which do not respond to the orthodox methods of treatment may be due to small impalpable granulosa-cell tumours of the ovary.

The symptoms of menstrual disturbance due to the tumours retrogress after their removal. Menstruation becomes normal and the patients may later bear children.

The fourth and fifth decades have been shown to be the periods when both the incidence of granulosa-cell tumour and liability to it are greatest. It is, therefore, not an infrequent occurrence to find a case of granulosa-cell tumour in which the menopause appears to have been an early one, possibly in the last years of the third decade. The grandulosa-cell tumour is discovered later, either during the period of amenorrhoea, or during a subsequent period of uterine haemorrhage. The early menopause in such a case may thus be not a true menopause, but a period of amenorrhoea occurring late in active sexual life, and due to a granulosa-cell tumour.

(3) *After the menopause.* The symptom which most frequently announces the presence of a granulosa-cell tumour in post-menstrual life is uterine bleeding. This may be regular, resembling normal menstruation, or irregular, and is usually excessive. It may occur in patients long past the menopause.

Uterine bleeding is also found, and much more frequently, in cases of uterine neoplasm, and, more rarely, in conjunction with other ovarian tumours, so that it is by no means diagnostic of granulosa-cell tumours of the ovary. Te Linde,[25] in a paper on

post-menopausal uterine bleeding, states that of 179 cases, 6.7 per cent (12 cases) were due to ovarian causes, and of these 1.1 per cent (2 cases) were due to granulosa-cell tumour. The number of cases of post-menopausal bleeding due to granulosa-cell tumour is thus very small.

Sarcomata of the ovary are sometimes described as having given rise to post-menopausal bleeding. Ovarian fibromata may cause post-menopausal haemorrhage as a result of mechanical obstruction, but do not cause uterine hyperplasia. Te Linde[25] also found that 40 per cent of cases of post-menopausal haemorrhage were of non-malignant origin. Fahmy[44] described 56.8 per cent of cases as having a non-malignant cause, and Geist and Matus[93] found 42 per cent with non-malignant causes. Fahmy's[44] statement was based on an analysis of 937 cases of post-menopausal haemorrhage. He mentioned Kanter's and Klawans's[94] report of 68.4 per cent of cases of post-menopausal haemorrhage as being of malignant origin.

Schiffman[95] described cases of various types of ovarian carcinoma which gave rise to uterine bleeding. Persistent post-menopausal bleeding not due to carcinoma of the cervix is usually due to carcinoma of the body of the uterus. Scanty bleeding of short duration usually has a non-malignant aetiology, and may be due to an endometrial polyp, or to chronic endocervicitis. Bleeding resembling menstruation in its regularity is very suggestive of granulosa-cell tumour. As with uterine haemorrhage occurring before puberty in cases of granulosa-cell tumour, post-menopausal bleeding of the same origin is not dependent upon ovulation, but is probably due to regular periodic drops in the level of oestrin in the blood.

Patients who develop granulosa-cell tumours after the menopause frequently notice enlargement of the breasts, and Meyer[41] describes galactorrhoea occurring in two patients aged 61 and 70 years respectively, both of whom were found to have granulosa-cell tumours. Novak[96] describes an interesting case of granulosa-cell tumour in a woman of 57 years of age. The patient had passed through a normal menopause at the age of 47, and for 6 months before being seen had had uterine bleeding resembling normal menstruation, lasting 3 or 4 days, and recurring at 4-weekly intervals, accompanied by the usual menstrual molimina. The last attack of bleeding was 24 days before the operation. She stated that she felt rejuvenated. On examination, the uterus was found to be the size of a 2-months' pregnancy. The adnexa were not enlarged. Curettage

revealed a hyperplastic, polypoid, non-malignant endometrium, and granulosa-cell tumour was suspected. Total hysterectomy and bilateral salpingo-oöphorectomy were performed. The right ovary was senile; the left ovary contained a round solid yellow tumour, 1.5 cm. in diameter at one pole; and the uterus had a polypoid endometrium and several small interstitial myomata.

The ovarian tumour was a sarcoma-like granulosa-cell tumour, with tubular and strand-like arrangements of cells in the peripheral parts. These were said to be characteristic of granulosa-cell tumour. The patient was well when seen a few months after the operation, and stated that since then she had passed through a second menopause with severe vaso-motor symptoms.

The foregoing account of the symptomatology of the granulosa-cell tumour in the three divisions of the sexual life of woman shows that atypical uterine bleeding is the chief symptom of its presence. A preceding period of amenorrhoea caused by the tumour cannot be identified in tumours occurring before puberty and after the menopause. At whatever period of life the tumour may occur, its removal causes the symptoms to recede, and the patients to return to normal.

Rate of Growth of the Tumour.

Definite information is not available, but the tumour is probably a slowly growing one. This hypothesis is suggested by the length of time menstrual disturbances are noted before the tumour is removed, in cases which occur during active sexual life. A few years' history of amenorrhoea or irregularity, following upon regular menstruation is very common.

Complications.

Torsion of the pedicle of the tumour is said by Te Linde[19, 20] to be rare. It occurred in 1 of the 7 cases reported by Lepper, Baker and Vaux[21] and the tumour was found at the operation for acute abdominal emergency.

Haemorrhage into the cystic areas of the tumour is common, but appears rarely to give rise to symptoms.

Sterility being a very probable symptom of the tumour, obstruction of labour as a result of granulosa-cell tumour is not described.

Ascites is not often found, but is not particularly suggestive of malignancy. It occurs in association with various other benign ovarian tumours, particularly with fibromata of the ovary. In

the case of Klaften's[82] of a child aged 4 years, there were found to be 2 litres of ascitic fluid.

Associated Pathological Conditions.

The association of another benign ovarian tumour such as pseudomucinous cyst, or fibroma in the same ovary, with a granulosa-cell tumour is not very uncommon, and has been discussed on page 885. The accompanying uterine changes have been described.

Differential Diagnosis.

At any period of life, the association of an ovarian tumour with uterine bleeding and with endometrial cystic hyperplasia, as revealed by curettage, is strongly suggestive of granulosa-cell tumour. This reaction of the uterine endometrium to the presence of a granulosa-cell tumour of the ovary is an important diagnostic point. Kleine[45, 81] goes so far as to say that glandular hyperplasia of the endometrium in association with an ovarian tumour is pathognomonic of granulosa-cell tumour, especially when the patients concerned are children or elderly women. Diagnostic curettage should be performed in all doubtful cases.

Cases occurring before puberty can usually be diagnosed in this way, and the same relative ease of diagnosis by the same methods applies to cases occurring after the menopause.

Curettage will distinguish the cases of post-menopausal haemorrhage due to uterine carcinoma from those due to uterine hyperplasia occurring as a result of granulosa-cell tumours.

It is during the period of active sexual life that the diagnosis is most likely to be uncertain.

At this period, ectopic gestation must be considered in the differential diagnosis. In both cases there will be unilateral adnexal swelling, an enlarged uterus, amenorrhoea, or amenorrhoea followed by uterine bleeding. The oestrin content of the urine is at a high level in pregnancy and is probably high in granulosa-cell tumuor. The Zondek-Aschheim test is positive in ectopic pregnancy and negative in granulosa-cell tumour. The previous history of the patients is valuable in such cases, the history of menstrual disturbances being longer in cases of granulosa-cell tumour than in cases of ectopic gestation. Laparotomy makes the diagnosis obvious.

The diagnosis of a small granulosa-cell tumour from a follicular cyst, in a patient with symptoms of metropathia haemorrhagica may be very difficult. The history is usually longer in cases of

granulosa-cell tumour, especially when a period of amenorrhoea forms part of the symptomatology. The endometrium may present the same picture in either case.

Uterine fibroids may be mistaken for granulosa-cell tumour, especially when they cause menstrual disturbances.

In overcoming the difficulty of pre-operative diagnosis of granulosa-cell tumour, the most important factor is that the surgeon should have this condition in mind, and should thus be able to include granulosa-cell tumour as a possibility in any doubtful case.

Recurrence.

Recurrence of a neoplasm is usually regarded as being just as good a proof of malignancy as is metastasis. There are, however, a few cases of granulosa-cell tumour described in which the recurrence of the tumour occurred in the other ovary and was apparently non-malignant in nature. This was found in Rummeld's case[78] of granulosa-cell tumour with recurrence in a child of 5 years. The child was well 10 years after removal of the second tumour, so that it is very unlikely to have been a malignant one. In Bland's and Goldstein's case[61, 62, 63] of a child of 7 years of age, a granulosa-cell tumour recurred in the other ovary. The after-history available is only 6 months after the second operation, but up to that time the child remained perfectly well.

The occurrence of properly demarcated recurrences without peritoneal invasion or ascites is not found with malignant ovarian tumours, in which generalized peritoneal metastases are the rule.

Von Werdt,[18] Klaften,[46] and Fauvet[75] have each described cases with retroperitoneal recurrences in which the removal of the recurrent tumour gives as good a chance of recovery as did removal of a primary non-malignant tumour. In Klaften's case,[46] the retroperitoneal tumour occurred 10 years after the removal of a granulosa-cell tumour of the ovary. It was of the same type as the first tumour, and Klaften[46] regards it, not as a metastasis, but as an independent tumour having formed possibly in ectopic ovarian tissue. The length of the interval between removal of the ovarian tumour and occurrence of the retroperitoneal tumour is considered by Klaften[46] to be too great for the second tumour to be considered as a metastasis. The patient was 29 years old at the time of the first operation, but had never menstruated. Regular menstruation set in only a year after operation, and she had 1 child. There was amenorrhoea for 3 years before

the second operation, alternating later with continuous bleeding. Menstruation returned 5 months after the second operation. The mammary glands had grown before the first operation, and secretion could be pressed from them.

Schiller[24] also suggests that such cases of non-malignant recurrence are to be regarded rather as newly formed and independent tumours of the same type as the primary tumour. They have not, according to this view, any aetiological connexion with the primary tumour, but may be due to some inherent peculiarity in the patient which makes her liable to form these tumours. The retroperitoneal recurrences are ascribed by Schiller[24] to development of this type of tumour from retroperitoneal rests of embryonic mesenchyme.

Malignancy.

On clinical evidence, the large majority of typical granulosa-cell tumours, in cases the after-history of which is given, behave as non-malignant growths.

Kleine[45] considers that late metastases are characteristic of granulosa-cell tumours. He publishes cases in which the patients were found to be well for periods from 3 to 21 years after removal of the tumour. Klaften[46] suggests that the primary tumour inhibits the formation of distant metastases in the same way as mature follicles and corpora lutea appear to inhibit the maturation of other follicles in a normal ovary. Soltmann[97] describes a case of bilateral granulosa-cell tumours in a woman of 41 years of age, who died of paralytic ileus 10 days after operation for their removal. At autopsy, metastases were found in the first and second vertebrae. They resembled the primary growth, the only difference being that they showed complete absence of connective tissue. This communication is usually cited as showing that granulosa-cell tumours can metastasise to bone.

Novak[23] considers the malignancy of this type of tumour to be 28.1 per cent., and bases this figure on an examination of 32 cases of granulosa-cell tumour. As has been suggested, the malignant cases may have their origin from other than granulosa-cells. Novak[23, 96] bases some of his diagnoses on histological examination alone.

The number of years which have elapsed since operation after which a patient may be considered cured is a point on which various observers differ. In cases of carcinoma and sarcoma of the ovary, recurrence is usually found within a year of operation.

There is no recognized standard interval in the case of ovarian carcinomata, but Schiller[24] states that a 5-year cure is generally accepted as suitable for statistics of columnar carcinoma of the ovary. He says that recently French authorities have quoted cases, in which the patients were well 2 years after the operation, as being completely cured, in statistics of their operation successes. Taking a 5-year cure as a reasonably accurate standard, it is found that in many cases of granulosa-cell tumour in which such information is available the patients are well after this interval and for many years later. In 5 of the cases of Lepper, Baker and Vaux,[21] excluding the 1 patient who died 17 years after operation, more than 5 years have now elapsed since the operation and the patients are still perfectly well and free from recurrence.

Prognosis.

The prognosis of a typical granulosa-cell tumour, so far as can be at present ascertained, is uniformly good, the danger to life being no more than in any similar abdominal operation. Torsion of the pedicle of the tumour is the only dangerous complication, which renders immediate operative treatment for acute abdominal emergency necessary. Recovery is usually uneventful, and after removal of the tumour the patient returns to normal. Recurrence, a rare event, has been fully discussed.

Treatment.

Salpingo-oöphorectomy of the affected ovary is the treatment for a granulosa-cell tumour. Many such tumours are not recognized until after removal, and naked-eye appearances at operation have to be relied upon in order to determine the extent of the operation. If the tumour does not show any obvious signs of malignancy, such as necrotic change, adherence or metastases, and if it is possible or probable that it is a granulosa-cell tumour, a young patient should be given the benefit of the doubt, and only local removal of the growth should be undertaken. This involves the risk, in a few cases, of the necessity for operating again in order to do a radical removal of the pelvic genital apparatus, should the growth, on examination, prove to be a definitely malignant type of tumour. The tumour should be intensively examined microscopically, and the total urine passed during the first 48 hours after the operation should be collected in order that it may be tested for oestrin content, and so provide information on this subject.

In patients past the menopause, many surgeons will prefer to undertake a radical removal of the growth in the first instance, even though it is known or thought to be a granulosa-cell tumour, and even though such cases have been shown to recover after local removal of the growth. Such a procedure obviates the risk of having to re-open the abdomen to perform a radical operation, and avoids the possibility of recurrence, or of the development of another similar growth in the other ovary, an event which has, however, been shown to be very rare.

The equally well maintained recovery of reported cases in which patients were treated by unilateral salpingo-oöphorectomy and those who were treated by total hysterectomy and bilateral salpingo-oöphorectomy shows that the radical operation is not necessary in order to effect a cure. There is no indication of any tendency to malignancy as the age of the patient increases, and conservative treatment may, therefore, safely be recommended in all cases.

Novak[23] suggests that unilateral salpingo-oöphorectomy should be performed in young patients, but that total hysterectomy and bilateral salpingo-oöphorectomy are advisable in elderly patients with granulosa-cell tumours. He recommends the restriction of radiotherapy to inoperable or recurrent tumours, and urges associated surgical treatment when possible. Kleine[45, 81] states that granulosa-cell carcinomata, if incompletely removed, may be successfully treated radiologically. He states that tumours described as malignant granulosa-cell tumours have marked radio-sensitivity, and draws an analogy between the radio-sensitivity of the normal follicular epithelium and that of the granulosa-cell tumour. He lays down the principle that all reports of results of radiotherapy of ovarian tumours should always include exhaustive histological findings in order to render the conclusions valuable. Schulze[65] describes a case of granulosa-cell tumour in a woman of 54 years of age who had been treated by radium 4 years previously on account of menorrhagia. She considers that the growth of the granulosa-cell tumour may have been inhibited by the radium treatment. Schiller[24] considers that post-operative radiotherapy is unnecessary. The results of application of radiotherapy to these tumours is little understood, and more reports are necessary before its value can be assessed. Conservative surgical treatment can offer complete cure, with return of the patient to normal, and post-operative radiotherapy in cases of granulosa-cell tumour would appear to be unnecessary.

Untreated cases of granulosa-cell tumour are practically un-

known. Brenner[15] found one of his cases in a woman at post-mortem, but apart from such a rare finding, reports are not available, and there are not any data to show what may happen if these patients are allowed to go untreated.

Conclusions.

The fact that malignant tumours derived from the granulosa may, and probably do exist, is not denied, but the opinion is held that there are not as yet any certain means of distinguishing the malignant granulosa-cell tumour from primary or secondary malignant ovarian tumours which may resemble it histologically but which are not derived from the granulosa. This opinion is based upon a consideration of the clinical after-histories of reported cases. This method alone is able to show whether the tumour is malignant or non-malignant, whatever the histological appearance may be.

The patient from whom a granulosa-cell tumour has been removed should be encouraged to present herself for examination at regular intervals, both for her own benefit and also in order to swell the amount of clinical evidence which at present exists regarding the after-histories in cases of these interesting growths. This is especially necessary in order that the controversial question of the malignancy of these tumours may be settled, on clinical grounds.

Granulosa-cell tumours, though rare tumours, will almost certainly be found to occur in larger numbers than heretofore, as their clinical and histological characteristics become more widely recognized. Pre-operative diagnosis of these tumours is possible in many cases on the clinical history and findings on examination of the patients alone. Diagnostic curettage reveals cystic hyperplasia of the endometrium. Examination of the urine for oestrin may become a valuable and important aid to diagnosis. Many more observations on the production of oestrin by these tumours are required in order that our knowledge of their endocrine action can be systematized.

The clinical action of this tumour upon the patient, and the results of endocrine investigation, so far as they go, alike suggest that in the granulosa-cell tumour we are dealing with yet another example of those tumours which are capable of the production of hormones similar to or identical with those normally elaborated by the organs from which the tumours arise.

SUMMARY.

1. Typical granulosa-cell tumours of the ovary are unilateral, soft solid, or partly solid and partly cystic, encapsulated, and vascular. The surface on section is pinkish or fleshy in colour, or bright yellow.

2. They fall into three main histological groups, with transitional forms between these: (1) folliculoid; (2) diffuse or sarcomatoid; (3) cylindoid or trabecular. In addition, the oöphoroma folliculare or Brenner tumour is probably a variety of granulosa-cell tumour. In all of them the component cells resemble follicle cells at various stages from primordial follicle to mature granulosa about to be luteinized.

3. The uterus in cases of granulosa-cell tumour is enlarged to the size of a 2 to 3 months pregnancy, and the endometrium shows cystic hyperplasia.

4. Such after-histories as are available indicate that the majority of typical granulosa-cell tumours are non-malignant, though the histological picture often suggests malignancy. Some malignant tumours described as granulosa-cell tumours may be misdiagnosed as such.

5. They may occur at any age of life. The greatest incidence and liability to these tumours is between the ages of 40 and 60, i.e. about the menopause. The greatest incidence of the Brenner tumour is between 60 and 70 years of age.

6. In childhood they cause precocious puberty with uterine bleeding. In active adult sexual life they cause menstrual irregularity, or amenorrhoea followed by uterine bleeding, which may be regular or irregular and is usually excessive. After the menopause they cause post-menopausal uterine bleeding, which may be regular, resembling normal menstruation.

7. The tumours probably produce large quantities of oestrin. This is thought to be the cause of the hyperplasia of the uterine endometrium. The symptoms, other than mechanical ones due to the presence of an ovarian tumour, probably depend on this production of oestrin.

8. Treatment is unilateral salpingo-oöphorectomy of the affected ovary, more radical removal being necessary only if clinical evidence of malignancy is obvious at the time of operation. The prognosis is good and this treatment promises return of the patient to normal in every way. Post-operative radiotherapy is not indicated.

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British College of Obstetricians and Gynaecologists

THE Quarterly Meeting of the Council was held in the College House on Saturday, July 24th, 1937, with the President, Sir Ewen Maclean, in the chair.

Sir Ewen Maclean, LL.D., M.D., M.Sc., F.R.C.P., Hon. F.A.C.S., was re-elected President; Robert William Johnstone, C.B.E., M.A., M.D., F.R.C.S.E., and Miles Harris Phillips, M.D., F.R.C.S., Hon. M.D., were elected Vice-presidents; Eardley Lancelot Holland, M.D., F.R.C.P., F.R.C.S., honorary treasurer; Sir Comyns Berkeley, M.A., M.D., M.C., F.R.C.P., F.R.C.S., Honorary Appeal Treasurer; William Fletcher Shaw, M.D., Hon. F.A.C.S., Honorary Secretary; Frederick Roques, M.A., M.D., M.Ch., F.R.C.S., Honorary Librarian.

Admitted to the Fellowship of the College:

Sir Mangaldas Vijbhucandas Mehta	Bombay, India

The following were admitted to the Fellowship of the College (*in absentia*):

Doris Clifton Gordon	Stratford, New Zealand
Stephen Langevin	Montreal, Canada
John Arthur Hopkins	Sherwin, Melbourne, Austral.

The following were admitted to the Membership of the College:

John Robertson McArthur	Toronto, Canada
William Leonard Maccormac	London
William Ian Clinch Morris	Ayr
Dudley Clifford Racker	Manchester
Stanley William Wright	Newcastle, Staffs.

The following was admitted to the Membership of the College (*in absentia*):

Arthur Lionel Gilbey	Portsmouth

The following were elected to the Membership of the College:

M. C. Albuquerque	Bangalore, India
Eric Bailache	Melbourne, Australia
Sudhir Chandra Bose	Calcutta, India
Marjorie Ruth Elizabeth Boyd	Dublin
Francis Joseph Burke	Liverpool
Hugh Callagher	Melbourne, Australia
Isabella Douglas Cameron	London
Henry Canwarden	London
Mrs. D. J. P. Dadabhoy	Bombay, India
Jagadia Pada Dutt	Calcutta, India
Edith Ghosh	Calcutta, India
V. B. Gokhale	Belgaum, India
Hartley Frederick Patterson Grafton ...	Hamilton, Canada
Charles John Kenneth Hamilton	Liverpool
M. R. W. Hart	Madras, India
Allan Frederick Hollinrake	Hamilton, Canada
Meher Homji	Bombay, India
John Howkins	London
John Godfrey Hastings Ince	London
Mary John	India
James Walter Johnstone	Korumburra, Australia
R. A. Logan	Nagpur, India
Poonen Lukose	Travancore, India
Anna P. Martin	Nagpur, India
L. de Menezies	Nagpur, India
E. Achyutha Menon	Waltair, India
Dhirendra Nath Mitra	Bengal, India
Mrs. Monohan	Madras, India
Una Morton	Agra, India
Bamandas Mukherjee	Calcutta, India
Herbert Murray	Calcutta, India
A. N. Palit	Bihar, India
N. A. Purandhare	Bombay, India
Peter William Stewart Riley	New Zealand
Akhilanath Sarkar	Patna, India
Manindra Nath Sarkar	Calcutta, India
George Albert Simpson	Sernia, Canada
Bawa Harkisham Singh	Bengal, India
Arnold Bernard Stenhouse	London
Rivavarma Kunjam Keralavarma Tampan	Edgmore, India
P. Venkatagri	Madras, India
Margaret Venters	Manchester
Robert James Wotherspoon	Glasgow

BOOK REVIEWS.

"Gynaecology for Nurses." By H. S. Crossen and R. J. Crossen.

This well-produced book is evidently written by gynaecologists who are sufficiently interested, and also able, to assist a nurse so to understand the help she can give them, that the maximal efficiency may be the result of her efforts.

The clear, concise sentences in which elementary knowledge of points in anatomy and physiology are given, form an excellent introduction to Part I. The remainder of this section contains only a brief survey of gynaecological conditions, and their treatment, but the numerous descriptive illustrations of diseased conditions and also of operative procedure should be invaluable in assisting nurses to the acquisition of very considerable knowledge.

Part II contains detailed information of the preparation of patients for examination, treatment, and operation, on the preparation of theatre stores and instruments and the routine of operation-room technique; and on the care a nurse should have of her patient in the operation room and, afterwards, in her post-operation nursing care. Many practical nursing points are introduced, the psychological approach of nurse to patient is considered, and the importance of accurate nursing observation emphasized. Nurses should find this book not merely instructive but inspiring.

M.C.P.

"Synopsis of Obstetrics and Gynaecology," by Aleck W. Bourne, M.A., M.B., B.Ch. (Camb.). F.R.C.S. (Eng.), F.C.O.G. (Seventh edition.) Bristol: John Wright & Sons Ltd. 452 pp. Price 15s.

The fact that seven editions of this book have been called for since its first appearance in 1913, when "Gynaecology" was not included, is witness enough of its worth and popularity.

The work appears in the familiar blue covering and the matter is divided into the two main sections of its title; in each case the arrangement of the material is on conventional lines and is so strictly grouped under headings and sub-headings, with appropriate type, that reference to any point is easy.

The matter is clearly and shortly put in a manner that does not admit of any misunderstanding, and this will continue to be of great benefit to that public to which the volume is particularly addressed, the student preparing for examination and the lecturer wishing to refresh himself on a particular point.

One criticism is that, with everything epitomized, perspective is apt to be rather blurred. Thus, in discussing the treatment of puerperal sepsis a formidable list of operative procedures is described and the value of conservatism is not perhaps sufficiently emphasized; the same may be said in the case of antepartum haemorrhage, although any of these operations may be justifiable or even necessary in selected cases.

The line illustrations at the foot of so many of the pages definitely add clarity to the letterpress.

Every effort has been made to bring the subject-matter up to date as is shown by the account of prontosil in the treatment of puerperal sepsis, while the recent knowledge concerning the mechanism of menstruation and the influence of the various ovarian and pituitary hormones on that function is clearly stated. In discussing the hormone treatment of functional conditions such as menorrhagia appropriate information is shortly indicated, but the author is cautious, temperate, and does not make any extravagant claims for this line of treatment, which is obviously only in its early stages.

In the preface it is pointed out that the description of methods of artificial respiration in the condition of shock in the newborn, white asphyxia, is now omitted; this is a welcome omission which could be followed with advantage by certain other writers who so frequently describe in detail methods of resuscitation which could result only in depriving the child of its last chance of existence.

It would be unfair to criticize, from a personal point of view, certain details in a work which does not aim at originality, rather the reverse, and the volume can in general be thoroughly recommended as a concise and sane exposition of obstetrical and gynaecological practice in this country at the present time.

G.I.S.

"Diathermy," by ELKIN P. CUMBERBATCH. Third edition.

THE third edition of Dr. Cumberbatch's "Diathermy" which was published in March is a larger volume than its predecessors, for in addition to the new material added by the author, there are articles contributed by 9 other workers, each of whom has written on a subject in which he has had special experience. As a result, the book has gained considerably in interest, and the articles written by surgeons give it an authority which has hitherto been lacking in books in which surgical methods have been described only by the electrologist.

In the present volume, the chapter contributed by C. A. Robinson will be of particular interest to gynaecologists, for the author describes in detail his original treatment of pelvic infection which has given such good results. As the temperature which is lethal to gonococci is low, the object of the treatment is to heat the infected tissues to a temperature of about 115°F., and in addition to the lethal effect obtained, another result of diathermy will be to raise the bactericidal power of the serum and leucocytes. A specially designed cervical electrode is used in treating cervical infection, a pliable metal belt acting as the indifferent electrode. Temperature and dosage can be definitely controlled with careful technique and the curative results are distinctly good. In all cases, Dr. Robinson advises a preliminary course of general pelvic treatment, which is effective in diminishing the toxaemia, before the more localized cervical treatment is commenced. The general pelvic treatment is applied through a fairly large vaginal electrode and a metal belt similar to that used when treating the cervix.

Short-wave therapy and artificial-fever therapy have also been used in

gonococcal infections; in the former the results are uncertain and the dosage uncontrolled, while the latter is arduous treatment for both patient and operator which can only be undertaken by in-patients.

Among other chapters of special interest is one on surgical electrothermic methods in diseases peculiar to women. Notes are given of cases in which inoperable malignant disease of the breast has been treated by surgical diathermy, and of cases of eradicable tumours in which the cutting arc has been used in preference to the scalpel. Cases are also mentioned in which diathermy coagulation of cervical carcinoma was carried out as a preliminary to hysterectomy.

The chapters on diathermy in ophthalmology and in oto-rhino-laryngology will be of general interest and those on short-wave therapy and inducto-therapy will be new to many. The new edition of Dr. Cumberbatch's book maintains the high standard of the earlier editions and is greatly increased in comprehensiveness.

C. B. Heald.

Review of Current Literature.

Director: FREDERICK ROQUES, M.A., M.D., M.Chir. (Cantab), F.R.C.S., F.C.O.G.

THIS Review contains the lists of contents and abstracts of the more important articles from the following journals with which the "Journal of Obstetrics and Gynæcology of the British Empire" exchanges :—

British.—The Lancet; British Medical Journal.

Canadian.—The Canadian Medical Association Journal; Bulletin Médical de Quebec.

Australian.—Medical Journal of Australia; The Australian and New Zealand Journal of Surgery.

Indian.—The Calcutta Medical Journal.

American.—American Journal of Obstetrics and Gynecology; The Journal of the American Medical Association; Surgery, Gynecology and Obstetrics; American Journal of Diseases of Children.

French.—La Gynécologie; Gynécologie et Obstétrique; Bulletin de la Société d'Obstétrique et de Gynécologie de Paris.

Belgian.—Bruxelles Médical.

Italian.—Annali di Obstetrica e Ginecologia; Archivo di Obstetrica e Ginecologia; Revista Italiana di Ginecologia, Bologna.

German.—Archiv für Gynäkologie; Zeitschrift für Geburtshülfe und Gynäkologie; Zentralblatt für Gynäkologie; Monatsschrift für Geburtshülfe und Gynäkologie; Münchener Medizinsche Wochenschrift; Monatsschrift für Krebsbekampfung.

Scandinavian.—Acta Obstetrica Scandinavica.

South American.—Boletin de la Sociedad Obstetricia y Ginecologia de Buenos Ayres.

Japanese.—Japanese Journal of Obstetrics and Gynæcology.

The Review of Current Literature thus keeps the readers of the Journal in touch with current literature throughout the world. At the end of the year an Index of all the subjects contained in the articles of the above journals is printed. Arrangements are also made to include abstracts of important articles on border-line subjects, such as Physiology, Biology and Biochemistry.

LIST OF ABSTRACTORS.

London: J. BEATTIE, F.R.C.S.; A. C. BELL, F.R.C.S.; R. K. BOWES, F.R.C.S.; J. LYLE CAMERON, F.R.C.S.; A. H. CHENARD, M.B.; B. GILBERT, Esq., F.R.C.S.; R. C. LIGHTWOOD, M.D.; J. A. MOORE, M.B.; C. D. READ, F.R.C.S. (Edin.); F. ROQUES, F.R.C.S.; R. WINTERTON, F.R.C.S.

Huddersfield: W. E. CROWTHER, M.B.

Leeds: R. H. B. ADAMSON, M.D., AND B. JEAFFRESON, F.R.C.S.

Liverpool: M. DATNOW, M.D.; P. MALPAS, F.R.C.S.; T. N. A. JEFFCOATE, F.R.C.S.

Manchester: R. NEWTON, M.D.

Glasgow: JANE H. FILSHILL.

The Lancet.

Vol. ccxxx, No. 5,878, February 1st, 1936.

*Use of analgesics by midwives. Report of an investigation by the British College of Obstetricians and Gynaecologists.

Vol. ccxxx, No. 5,878, March 28th, 1936.

*Carcinoma of the cervix uteri treated by the Stockholm Technique at the London Hospital. Alan Brews.

Vol. ccxxx, No. 5,876, April 11th, 1936.

*Neuritis in pregnancy successfully treated with vitamin B. G. W. Theobald.

Vol. ccxxx, No. 5,878, April 25th, 1936.

*Induction of labour for disproportion. J. H. Peel.

Vol. ccxxx, No. 5,880, May 9th, 1936.

*The effect of oestrin on the pituitary gland. W. Cramer.

*The cause of hypertension in pre-eclamptic toxaemia. Gladys H. Dodds.

*Unsuspected placenta praevia and post-partum haemorrhage. Douglas M. Lindsay.

Vol. ccxxx, No. 5,881, May 16th, 1936.

*Puerperal surgical scarlet fever. A. H. G. Burton and J. H. Weir.

*The treatment of vesico-vaginal fistula, with special reference to implantation of the ureters. G. Stewart Woodman.

Vol. ccxxx, No. 5,882, May 23rd, 1936.

*Anaemia in pregnancy. John A. Boycott.

Vol. ccxxx, No. 5,883, May 30th, 1936.

*The diagnosis of carcinoma of the cervix in the very early stages. Walter Schiller.

Vol. ccxxxi, No. 5,888, July 4th, 1936.

*Inhibition and induction of uterine bleeding by means of oestrone. S. Zuckerman.

*Trichomonas vaginitis. Ambrose J. King, W. Neville Mascall, and I. N. Orpwood Price.

Vol. ccxxxi, No. 5,891, July 25th, 1936.

Nitrous oxide and oxygen anaesthesia in the treatment of eclamptic fits. Theodore W. Allen.

Vol. ccxxxi, No. 5,893, August 8th, 1936.

Decreases in the gonadotropic hormone production during pregnancy. W. R. Henderson and J. M. Robson.

Vol. ccxxxi, No. 5,895, August 22nd, 1936.

*Sterile mating. V. B. Green-Armytage.

Thrombophlebitis in obstetrics and gynaecology. Stephen K. Westmen.

Vol. ccxxxi, No. 5,899, September 19th, 1936.
*Some problems in antenatal supervision. Gilbert I. Strachan.

Vol. ccxxxi, No. 5,904, October 24th, 1936.
Acute inversion of the uterus following ventral fixation. John Lankester.

Vol. ccxxxi, No. 5,905, October 31st, 1936.
Constructive hygiene in obstetrics. John S. Fairbairn.

USE OF ANALGESICS BY MIDWIVES.

This is a report of the investigation undertaken by the British College of Obstetricians and Gynaecologists, at the request of the National Birthday Trust Fund. The various anaesthetics investigated were nitrous oxide and air, chloroform, and paraldehyde. With regard to gas and air, the investigations showed that the Minnitt apparatus is safe for use by midwives in hospital, but that it should be restricted to those midwives who have had a special training in its use and have shown themselves capable of managing it. The analgesia is satisfactory in a high proportion of cases, but as there is occasional restlessness, another person should always be present at the time of administration. Unfortunately, these requirements contra-indicate the suitability of the apparatus for domiciliary practice, as do its weight, bulk, and tendency to mechanical fault. Lastly, the cost, both of the machine and the nitrous oxide, will have to be considerably reduced, before its extensive use can be possible.

With regard to chloroform, three types of administration, chloroform capsules, the Mennell inhaler, and the Christie Brown inhaler, were investigated in nearly 5,000 cases. In these the maternal mortality-rate was 1.2 per thousand, and investigation of the six deaths shows that chloroform was directly responsible for death in 1 case, and that it was probably an important factor in the fatal issue in 2 cases.

The interference rate was 5.3 per cent, showing that there was no increase in interference as a result of the use of chloroform, a similar result was found with nitrous oxide and air. Analgesia was satisfactory in the majority of cases by all methods, but the committee feels that chloroform by any method should not be used by midwives acting alone.

THE TREATMENT OF CARCINOMA OF THE CERVIX UTERI BY THE STOCKHOLM TECHNIQUE AT THE LONDON HOSPITAL.

This paper is the result of the investigation of 71 cases treated at the London Hospital during the 2 years 1929 and 1930. Four patients were treated by operation, and of these 2 died, 1 was well 20 months afterwards, and the last is well 5 years after operation. Of the remainder, all treated by radium, there was a 5-year-cure rate of 24 per cent, as compared with the average cure rate of 23.8 per cent during the previous 10 years.

NEURITIS IN PREGNANCY SUCCESSFULLY TREATED WITH VITAMIN B.

Five cases of neuritis occurring in the later weeks of pregnancy are described; all were characterized by pain, tingling, and numbness in the arms and legs. Following the author's well-known view that this disorder is of

nature similar to beri-beri, they were all treated with vitamins. As a result 4 of the cases were completely relieved merely by the addition of vitamin B_1 to their diet; this result bears out the original thesis. The number of cases, however, is a somewhat small one, and it will be interesting to follow further experiments in this field.

Induction of Labour for Disproportion.

Peel's paper is of particular importance in view of the discussion at present raging about the subject. It is a careful analysis of 100 cases of surgical induction for disproportion. Of these the total stillbirth rate was 14 per cent, and the forceps rate 23.3 per cent, with 1 maternal death.

The conclusions suggested are that in primigravidae the induction of labour plays no part in the treatment of minor degrees of disproportion, on account of the high maternal mortality and morbidity involved, and the correspondingly high foetal mortality. In multiparae, on the other hand, the fact that labour can be induced by rupture of the membranes, a comparatively safe procedure, makes this method less advisable in a good many cases, particularly as the birth canal has been previously dilated.

The whole question of whether labour should be induced for disproportion in primigravidae is still under discussion; in multiparae there is fortunately more general agreement. On the one hand there is no doubt that the theoretical advantages are considerable, mainly the avoidance of Caesarean section. But until a *certain* manner by which the onset of labour can be guaranteed is evolved, the disadvantages and risks of ordinary surgical induction must contra-indicate the method in the majority of cases. Sepsis, uncertainty, high morbidity, and mortality, seem to be inseparable from its employment, even in expert hands, and though there are occasional cases in which it may be of value, its general employment is rapidly being superseded by trial labour.

The Effect of Oestrin on the Pituitary Gland.

Following the previous paper on the result of the administration of oestrin on the pituitary gland, the authors find that in addition to the chromophobe adenomata produced, a condition closely resembling hypophysectomy also results. Morphologically it produces hyperplasia of the anterior lobe of the pituitary, in which, however, the chromophil cells are greatly diminished, so that the enlarged anterior lobe consists mainly of chromophobe cells. There is also an intense congestion which may lead to haemorrhage in the anterior lobe together with an excessive production of colloid which sometimes permeates the anterior lobe. On the assumption that the chromophil cells are responsible for the production of the specific hormones of the anterior lobe, the general condition of hypopituitarism and the extensive changes in the other endocrine organs produced by oestrin find their explanation in this disappearance of the chromophil cells of the anterior lobe.

The Cause of Hypertension in Pre-eclamptic Toxaemia.

Of the three well-known signs of pre-eclamptic toxaemia it is probable that the hypertension is caused by a specific blood-pressure-raising substance

probably secreted by the pituitary gland. If this is so, the substance should be able to pass via the placenta into the foetal circulation, causing a rise in blood-pressure in the baby. To determine whether this is so, the authors haxe examined a number of cases, and have found that the infants of hypertensive mothers had not shown any similar rise of blood-pressure, and they concluded that the specific agent is not transferable.

Unsuspected Placenta Praevia and Post-partum Haemorrhage.

A case of placenta praevia giving rise to post-partum haemorrhage is described. The haemorrhage was extremely severe, and had all the usual characteristics except for contraction of the uterus throughout. The symptomatology is a rare one, and the case was only apparent after examination of the placenta.

Puerperal Surgical Scarlet Fever.

Three cases of puerperal pyrexia, 2 of which were proved to have scarlet fever, are described. In each case, although the typical sypmtoms of scarlet fever were present, no haemolytic streptococci were cultured from the throat, yet they could be easily obtained from the cervix. They all occurred in the practice of one medical practitioner, yet swabs from his throat were also negative. This proves, therefore, that the local lesion and point of entrance of the infection was the cervix. All the cases were much relieved by serotherapy, and it is suggested that in view of this outcome the same treatment should be adopted in all specific cases.

The Treatment of Vesico-vaginal Fistula with Special Reference to Implantation of the Ureters.

Fifty-four cases of vesico-vaginal fistula are described, 22 of which were treated by implantation of the ureters. Of these latter, 18 had Stiles's operation and the remainder Coffey's No. 2 or No. 3; the results appear to be generally excellent.

Anaemia in Pregnancy.

After a detailed study of 150 normal pregnant patients, the author found that there was less than 80 per cent of haemoglobin in 22 per cent. He concludes that: (1) The common anaemia of pregnancy in this country is of the hypochromic type and would appear to be due to iron deficiency. (2) Increase of blood-volume may cause an apparent anaemia in pregnancy by reason of the temporary fall in haemoglobin and red cells. Such a condition may be distinguished from a true anaemia by the blood-picture, but may co-exist with a true anaemia. (3) Anaemia is probably not a serious risk in pregnancy in this country. (4) The common anaemia of pregnancy responds well to adequate iron treatment unless there is complicating disease.

The Diagnosis of Carcinoma of the Cervix in a Very Early Stage.

This article is devoted to an explanation and description of Schiller's well-known iodine test for early carcinoma of the cervix. A good deal of

discussion has resulted following his original description, and though Schiller himself adheres to his belief that the test is a specific one, it must be admitted that some doubt still remains about its universal correctness.

INHIBITION AND INDUCTION OF UTERINE BLEEDING BY MEANS OF OESTRONE.

It is a curious phenomenon of endocrine research that different observers, both equally qualified, appear at times to obtain a contrary result from identical experiments. This has apparently been the case in the trials of oestrin, and this fact naturally has been much disputed. In this article Zuckerman has analyzed the recent work in this direction, and has been compelled to elucidate these variations by investigating the possible source of error. Correlating these with his own work he has arrived at certain definite conclusions with regard to the fact of the administration of oestrin during the menstrual cycle.

These are as follows: (1) Oestrin, when administered in adequate amounts throughout the menstrual cycle, delays the onset of the next menstruation. (2) Uterine bleeding will not occur during the course of daily injections of adequate amounts of oestrone either in normal or castrated subjects. It may occur if the daily dosage is of threshold or sub-threshold value, if the injections are too widely spaced, or if the absorption of the hormone is imperfect. (3) The available evidence does not suggest that oestrin actively stimulates uterine bleeding, but still favours the view that bleeding is an event which marks the cessation of the hormone's action.

TRICHOMONAS VAGINITIS.

The question of trichomonas infection of the vagina is by no means completely settled, and any contribution, such as the present one made after clinical study of the subject is doubly welcome. The authors have had the opportunity of a very considerable experience of venereal infection, and have recently made an investigation into 300 female patients with a view to determining the co-existence of gonorrhoea with trichomonas vaginitis. In this the trichomonas vaginalis was found to be present in 70, whereas it was co-existent with gonorrhoea in 31. They concluded that not only is the parasite very often found in association with the gonococcus in infection of the vagina, but that its presence adds considerably to the difficulty of identifying the gonococcus, the reason for this being that the parasite ingests the coccus. This would suggest that the conception of the trichomonas as a non-pathogenic parasite which only thrives on a previously damaged mucosa is correct, the gonococcus itself being the preliminary damaging agent.

STERILE MATING.

There are probably few gynaecologists who have had more experience of this subject than the author, and his observations are naturally both interesting and instructive. In spite of this, however, his statement that in 30 per cent of all cases the fault of non-conception lies in the male will not by any means be universally accepted, though his stress on adequate examination of the male partner will meet with general approval, in spite of the difficulties encountered.

In the female the commonest cause of primary sterility is genital hypoplasia, and this factor can account for about 40 per cent of all cases. It can be diagnosed by physical examination, or by a history of delayed onset of menstruation. Treatment is difficult and unsatisfactory if the cause is hormonal. Improvement, however, can generally be attained by attention to the general health, and the administration of anterior pituitary hormone and thyroid. The normal hydrogen-ion concentration of the vaginal secretion is also of importance. The figure for this is normally 4, and if the secretion is profuse it can rapidly immobilize the spermatozoa, whereas in normal circumstances its acidity is countered by the alkalinity of the sperm. Chronic cervicitis *per se* is not a very important factor in these cases, for however badly the cervix is damaged its secretion is always alkaline, and though inflammation of this area may produce sterility by the formation of mucous plugs, the obstruction is a purely mechanical one and can be relieved by dilatation.

Occlusion of the Fallopian tubes, is, strangely enough, responsible for sterility in only about 40 per cent of cases, in spite of the commonly held belief that the usual cause of sterility is gonococcal salpingitis. It is, however, the author's experience, and this will be confirmed by many gynaecologists, that occlusion is more commonly the result of abortion and septic pelvic infection. In this conclusion there will also be general agreement with the author's contention that lipiodol is of more value than insufflation, in spite of a variety of faults. The question of anovular menstruation is also of importance in this connexion, and there is no doubt that this type of bleeding is commoner than is generally thought. The condition can be diagnosed by curettage, and hormonal treatment is occasionally effective.

As a preventative, the author advocates,

(1) A complete physical examination of all men and women contemplating matrimony.

(2) Greater care of girls at puberty with a view to the prevention and treatment of hypoplasia.

(3) A more general knowledge of sex hygiene, and the maintenance of marriage advice clinics.

(4) Stern admonition against the use of contraceptives during the first few years of marriage, and the legal forbiddance of their sale without medical prescription.

(4) The abolition of the curette in the treatment of sterility and abortion.

(6) Investigation of both husband and wife after two years' fruitless marriage.

Some Problems in Antenatal Supervision.

It has long been a disappointment that maternal mortality has appeared to increase since the introduction of antenatal supervision.

The reasons ascribed are varied, such as that the supervision has been carried out by inexperienced persons, that it is insufficient in quantity and quality, and that the patients are irregular in their attendances. However that may be, it must be recognized that effective antenatal care is by no means so simple as was originally thought.

A great deal of stress, perhaps unnecessarily, has been, and is being

placed on pelvimetry, and as Strachan points out, there are many fallacies in these measurements. For example, it is notorious that considerable differences are registered by different competent observers measuring the same pelvis, while the varying amount of space taken by the muscles add to the practical impossibility of calculating accurate measurements. It is recognized by obstetricians that the absolute length of the interspinous and intercristal diameters is usually without significance, and it is pathetic how much faith is placed in this by so many doctors and nurses in charge of antenatal clinics; in fact, as Williams says, the fallacies of indirect mensuration are so great as almost to destroy its usefulness, particularly as regards the external conjugate diameter. It is, however, difficult to agree with the writer in his condemnation of the value of the diagonal conjugate. It is true, as he says, that there are very many fallacies in this examination. For instance, it is possible that the sacrum itself, rather than the promontory, may be felt, and varying degrees of prepubic fat may vitiate the measurements; but surely internal examination is one of our most valuable adjuncts. The pity is, as Aleck Bourne has repeatedly pointed out, that the measurement is usually limited to an attempt to touch the promontory with the fingers, the more valuable information which can be derived from a pelvic examination being wasted. We are aware that vaginal examination in the pregnant woman is often painful and usually distasteful, and that it is so full of fallacies that many prominent obstetricians have discarded its use altogether. For the experience of the majority has convinced them that routine examination about the thirty-sixth week, especially in primigravidae, is often of inestimable value in the prevention of many obstetric disorders. X-ray pelvimetry is rightly stressed, and it is regrettable that fuller use is not made of it by both the radiologist and obstetrician.

Albert Davis.

British Medical Journal.

No. 3,937, June 20th, 1936.

*Prevention of puerperal sepsis. Leonard Colebrook.

No. 3,946, August 22nd, 1936.

Maternity services. Sir Ewen Maclean.

The problems of the midwifery services from the standpoint of the country practitioner. R. E. Moyles.

Maternity services: the part played by the education of medical students. F. J. Browne.

No. 3,949, September 12th, 1936.

*Anaemia in poorer class women. Harold W. Fullerton.

Anaemia and toxaemia of pregnancy. Jocelyn Moore.

No. 3,950, September 19th, 1936.

*The anaemia of pregnancy. W. Carey Smallwood.

*Hypochromic anaemias of pregnancy ond the puerperium. Harold W. Fullerton.

No. 3,954, October 17th, 1936.

*Pulmonary tuberculosis and pregnancy. James Young.

Pulmonary tuberculosis and pregnancy. Henry Cohen.

No. 3,955, October 24th, 1936.

Maternity in its sociological aspects. Sir Henry Brackenbury.

No. 3,964, December 26th, 1936.

*Referred pain and in particular that associated with dysmenorrhoea and labour. G. W. Theobald.

No. 3,968, January 23rd, 1936.

*Variations of weight during pregnancy. M. D. Arwyn Evans.

PREVENTION OF PUERPERAL SEPSIS.

There are few authorities more qualified to write about puerperal sepsis than Colebrook, and his observations and suggestions for its prevention and cure make instructive reading. In reviewing a fatal case, he once more draws attention to his practical suggestions for the prevention of such tragedies. These suggestions postulate the need for:—

(*a*) An organisation of bacteriological services for detecting, before they give rise to puerperal infection, any potentially dangerous persons among those doing midwifery or in the household of the expectant woman—that is, those persons with inflammatory or catarrhal conditions of the respiratory tract due to the haemolytic streptococcus; for detecting at the earliest possible moment the cases of puerperal fever due to haemolytic streptococci, especially in maternity institutions; and for detecting a possible source of infection in such cases among the attendants, in order that they may not infect other patients.

(*b*) More provision for the immediate isolation of the streptococcus-infected puerperal fever cases when they occur.

(*c*) A definite policy of encouragement of certain types of maternity institutions and discouragement of others, according to the degree of safety from infection which each is judged to offer. Also, perhaps, as part of this policy, the conferment of powers giving opportunity for stricter supervision of certain types of institution which are regarded as potentially dangerous.

(*d*) A definite policy with regard to instruction in the use of masks and the most effective antiseptic precautions.

ANAEMIA IN POORER CLASS WOMEN.

This important paper deals with the adult female side in a large-scale investigation into the blood-counts of over 3,000 normal individuals of poorer class, and refers to several points of interest to the gynaecologist. In the first place it is known that the haemoglobin percentage in non-pregnant women falls gradually throughout reproductive life, and lies well below

the normal standard for women. After the menopause it rises, while in pregnant women it is 5 per cent below normal. Secondly, in the great majority of anaemic women the anaemia is due to a deficiency of iron, and this is borne out by chemical investigation of the food taken, which shows that the majority of women of the poorer classes are restricted to an iron intake which is much less than the accepted standard. The striking point, however, is that although the absorption of iron is less effective in older women, since the incidence of achlorhydria increases with age, the haemoglobin curve in women who have passed the menopause shows a marked rise, stressing the demands of pregnancy and menstruation.

The iron deficiency anaemia is apparently much more common among women of the poorer classes than the middle and upper classes, and is practically dependent upon economic circumstances. In addition, it appears to be proved that both pregnancy and menstruation in poor women cause demands for iron which are not compensated by the amount which can be procured from the diet.

The Anaemia of Pregnancy.

The anaemias of pregnancy are multifarious both in aetiology and manifestation, and it is this fault which has for so long been a stumbling-block. To overcome this primary difficulty, numerous different methods have been adopted by various authorities, but none has so far seemed to us entirely adequate. In this paper, however, a complete and succinct division is suggested, and though some of the inclusions appear a little superfluous, Smallwood's classification would appear to satisfy most of the desiderata.

In this the anaemias are divided into (*a*) physiological, (*b*) deficiency, (*c*) haemolytic, (*d*) post-haemorrhagic, (*e*) puerperal, and (*f*) others, with their appropriate subdivisions. They are discussed more fully in their separate divisions, and it is unnecessary here to describe each individually. The most important point, however, which has arisen out of these investigations is the finding that mild degrees of hypochromic anaemia of pregnancy are principally of the hospital patient type, and that though seldom dangerous to life, they are the cause of a good deal of maternal disability.

This type can usually be prevented or cured by ordinary routine therapy, but in addition there are occasional cases in which severe degrees of anaemia develop in the later months of pregnancy, and the writer suggests routine blood examination in the seventh month of pregnancy, and the most careful investigation of cases showing definite blood-changes.

Hypochromic Anaemias of Pregnancy and the Puerperium.

This paper records the results of an investigation similar to the one described above, with particular emphasis on the changes occurring as a result of the blood lost at parturition. The author found that while the average haemoglobin level falls during pregnancy, it rises slightly before delivery, while the rise is still marked from 48 hours to 1 year after that date. He is of the opinion that when the anaemia is marked, it has probably been present before pregnancy, but has been rendered more apparent

by physiological hydraemia. The conception, therefore, that uncomplicated pregnancy is found responsible for severe hypochromic anaemia should be discarded. With regard to the effect of parturition, it is well known that the haemorrhage at this time varies very greatly in amount and, if considerable, it appears capable of subsequently producing a most severe degree of hypochromic anaemia.

Pulmonary Tuberculosis and Pregnancy.

Of 46 cases of pulmonary tuberculosis in pregnant women investigated by James Young there was a total mortality of 30 per cent. The figure strikingly illustrates the devastating effect of pregnancy on the disease, and when it is recognized that in many cases the pulmonary condition had existed for years, and that death supervened fairly rapidly with pregnancy, the gravity of the combination is further emphasized. Similar figures to those of Young have been published by Robertson, Rist and others; yet in spite of this there is a number of physicians and obstetricians who believe that the danger has been exaggerated. It is difficult to understand this view, but it is possible, as Young says, that it has been influenced by the general feeling that consumptive women look better when they are pregnant. If this latter observation is true, it is difficult to understand how the disease should abate during pregnancy; perhaps the suspension of the loss of blood at menstruation, the increased rest and feeding, and the splinting of the diaphragm by the uterus are contributory factors. But, however that may be, there is no doubt that the puerperium is the most sinister feature of the problem.

With regard to prevention, it is certain that the women with the active disease should be dissuaded from marriage and conception until 3 years after the disease has abated. Sterilization is of value, but the problem of abortion is more difficult for it is certain that this may seriously imperil the patient's chance, for everyone is familiar with the tragic case in which galloping consumption follows an apparently straightforward evacuation of the uterus. James Young believes that the best method is to evacuate the uterus by abdominal hysterotomy under nitrous oxide anaesthesia. He claims for this that it is relatively bloodless and aseptic, and that it can also be combined with sterilization. In the reviewer's opinion, however, all these advantages can be gained, and the abdominal incision avoided by the adoption of the bloodless vaginal evacuation popularized by Green-Armytage and the writer. When properly carried out this method is a striking success, and it is a pity that it is not more widely known, for besides being speedy and bloodless it can be combined with vaginal sterilization.

Referred Pain and in Particular that Associated with Dysmenorrhoea and Labour.

The conception of this paper arose from the author's method of treating endocervicitis and erosions of the cervix by the introduction of a stick of silver nitrate into the cervix. He found that many patients complain of pain following the treatment, but that if the patient suffered from dysmenorrhoea the pain elicited was the same as that felt during menstrua-

tion and was occasionally of extreme severity. Theobald suggests that just as the nerve endings of the cervix can be stained by silver, so they are stimulated by the direct application of silver in the form of the nitrate stick. The pain was felt in the lower abdomen and could occasionally be relieved by local anaesthesia of the nerve endings of the first lumbar nerve; this suggested that the pain of dysmenorrhoea is likewise a referred pain which could be similarly relieved. With regard to the pains of labour, the author found that the abdominal pains are similarly referred along cutaneous nerves and may be completely abolished by infiltrating the ilio-hypogastric and ilio-inguinal nerve endings.

VARIATIONS OF WEIGHT DURING PREGNANCY.

This paper gives the results of a systematic examination of the variation of weight in pregnancy both in normal and toxic cases. It was found that the greatest average monthly gain was 4.8 pounds in primigravidae and 4.4 pounds in multiparae, the average gain in 159 cases being 4.5 pounds. In the toxaemic cases it was found that the average gain was greater, and it was concluded that an increase of 5 pounds, or more, per month is suggestive of toxaemia.

Albert Davis.

The Irish Journal of Medical Science

August 1936.

*A review of the methods at present used in the treatment of placenta praevia.

A REVIEW OF THE METHODS AT PRESENT USED IN THE TREATMENT OF PLACENTA PRAEVIA.

The author reviews the collected figures from four well-known maternity hospitals in England and Ireland. The maternal mortality was 45 per cent and the foetal mortality 56.5 per cent.

The best treatment of central placenta praevia is Caesarean section, if the surroundings are favourable. If this is not the case bipolar podalic version should be performed and bleeding prevented by pressure of the half breech.

W. R. Winterton.

The Canadian Medical Association Journal.

Vol. xxxvi, No. 6, June 1936.

*Puerperal infection. Ross Mitchell.

*Granulosa-cell tumour of the ovary with precocious menstruation. R. B. Hare.

PUERPERAL INFECTION.

Puerperal infection, the arch-foe of motherhood, is the greatest cause of maternal deaths. The condition was described by Hippocrates, Galen and Avicenna. White of Manchester in 1773, and Gordon of Aberdeen in 1795, were the first to reveal its contagious nature. Oliver Wendell Holmes, in 1843, in "The Contagiousness of Puerperal Fever" produced a classical essay.

Semelweiss, 1818 to 1865, was the first to establish the fact that the contagion of puerperal fever could be introduced from without and that the death-rate was definitely reduced when the hands of all, previous to examination, were thoroughly cleansed with chlorinated lime.

Pasteur further advanced the knowledge of the subject when he demonstrated that the streptococcus was at least one of the organisms of infection.

Lister, snatching at the new knowledge provided by Pasteur, introduced antiseptic technique with its offspring, aseptic procedure which brought modern obstetrics to its present scientific standing.

Munro Kerr states that fatal cases are due to streptococcus haemolyticus in 75 to 85 per cent; to anaerobic streptococci in 5 to 10 per cent. to penumococci, straphylococci aureus, bacilli coli, bacilli Welchii, etc., in 5 to 10 per cent. In grave and mild cases, the latter-named organisms is the cause in ascending frequency.

It has further been shown that streptococci may be divided into many serological groups, and it would appear that neither the vagina, bowel, perineal nor perianal skin harbour the more virulent types. These organisms, however, have been found on the hands and in the throats of normal individuals.

The placental site is believed to be primarily infected, producing septic endometritis. The more virulent types of organisms make their way through the lymphatics to the peritoneal surfaces causing peritonitis, local or general; parametritis; or to the connective tissues causing septic thrombophlebitis, from which the organisms may spread to the general circulation causing septicaemia or pyaemia.

Kneise, in 89 autopsies, found peritonitis in 43 cases, thrombophlebitis in 20 cases, pyaemia in 17 cases, and parametritis in 7 cases.

Prophylaxis is of the greatest importance. Examination and delivery should always be conducted with the same aseptic and antiseptic technique as applies to any major surgical operation. The attendants should be careful to cover the nose and mouth with 4-ply masks of fine meshed gauze.

All cases of puerperal sepsis must be removed at the earliest possible moment from the lying-in hospitals and all doctors and nurses with any throat infection or any respiratory disorder, such as a common cold, should be prevented from entering the labour room.

When infection does occur, the patient should be isolated and hygienic measures should be instituted. These include fresh air, sunlight, good nursing, simple, nourishing food, forced fluids, sleep and freedom from worry. Sterile glycerine may be instilled into the uterus because of its hygroscopic action inducing a flow of lymph from the uterine wall through the cavity. Drainage should further be ensured by keeping the patient in a sitting position.

Chemotherapy, which embraces the injection into the blood-stream of various antiseptic substances has been, on the whole, disappointing.

Repeated small blood-transfusions are advocated.

Cadham favours infusion with blood-serum, 60 to 100 c.c. of blood are placed for 12 to 18 hours on ice, the serum then being removed and infused on alternate days. Serum from immunized rabbits is injected on every other day, the rabbits having been injected with vaccine prepared from the organisms in the patient's blood. The inoculation is made in a series of rabbits already immunized to streptococci and staphylococci. The blood is withdrawn from the rabbit's heart, is allowed to clot, the serum is then removed and tested for sterility. The patient is then inoculated subcutaneously or intramuscularly with this serum.

Meanwhile the inoculation of the rabbits is continued daily. Occasionally, the serum is administered on successive days. It is important that it should be given as early as possible.

Up to February 1936 Cadham had thus treated 41 patients who were severely ill with puerperal septicaemia with 36 recoveries. This contrasts favourably with the average death-rate for puerperal sepsis with positive blood-culture, which is 85 per cent.

Operative treatment, such as drainage of parametric abscesses when fluctuation appears and by excision and ligation of the pelvic veins distal to the thrombi, when a diagnosis can be made, should be carried out; drainage when peritonitis has occurred is usually beneficial when the gonococcus is the infecting agent. It is, however, disappointing when the streptococcus is present.

Granulosa-cell Tumour of the Ovary with Precocious Menstruation.

A girl of 7½ years of age was seen because of vaginal bleeding. She appeared to be normal in size and mentality, but her breasts were enlarged and there was some pubic hair.

Rectal examination revealed a uterus twice the size normal for her age, and a right ovary considerably enlarged; the left ovary was scarcely palpable.

The first vaginal bleeding lasted 12 days. Three weeks after this another menstrual period began lasting 2 weeks. Abdominal operation was performed and the right ovary was found to be yellowish pink in colour and of the size and consistence of an adult testicle. The other ovary appeared normal.

The patient had previously suffered from rectal bleeding due to rectal polypi. The bowel at the time of operation was palpated and a small intussusception about 6 inches long was discovered and easily reduced. This was caused by a small polypus at the apex of the intussusception which was removed by enterotomy. The right Fallopian tube and the right ovary were removed; the patient made an uninterrupted recovery, although there was vaginal bleeding which gradually diminished and ceased at the end of the second week.

The excised ovary measured 5.5 by 4.8 by 4 c.m. and was almost entirely occupied by a solid golden yellow tumour measuring 3.9 centimetres in diameter. This tumour resembled a large solid corpus luteum of pregnancy but it had no haemorrhagic centre.

Microscopical examination showed that it was composed of gland and cord-like structures lined with large epithelial cells which were made of pale-staining vacuolated cytoplasm and relatively deeply-staining nuclei. The cells were arranged in glandular formation. Special staining showed that the epithelial cells were heavily laden with large droplets of fatty material.

The regular arrangement of the epithelial cells and their uniformity in size was strongly suggestive of non-malignant qualities. These cells were characteristic of those found in granulosa-cell tumours. The capsule was in every way intact. The Fallopian tube was normal except for an extra ostium.

J. Lyle Cameron.

Medical Journal of Australia.

Vol. xi, No. 16, October 17th, 1936.

*The treatment of cancer of the cervix uteri. H. H. Schlink and Clement Chapman.

Experiences in the treatment of cancer of the cervix uteri with radium and deep X-ray therapy. Hubert K. Porter.

Vol. xi, No. 20, November 14th, 1936.

Pyelitis and pyelonephritis. Acidification and mandelate therapy. R. J. Silverton.

Vol. xi, No. 22, November 28th, 1936.

The out-patient treatment of gonorrhoea in women. Beatrice Warner.

Gonorrhoea in the in-patient adult female. Kenneth J. G. Wilson.

Vol. i, No. 1, January 2nd, 1937.

Uteroscopy. Kenneth Addison.

Vol. i, No. 3, January 16th, 1937.

Some remarks on antenatal supervision. T. G. Wilson.

Some remarks on the relief of pain in childbirth. Brian H. Swift.

Vol. i, No. 4, January 23rd, 1937.

*Trichomonas vaginalis vaginitis as a cause of pruritus. Brian H. Swift.

Vol. i, No. 5, January 30th, 1937.

Midwifery since the time of Ambroise Pare. Alex. H. Marks.

Treatment of Cancer of Cervix Uteri.

A series of 203 cases of carcinoma of the cervix uteri treated during the last five years is described. When possible Wertheim's operation was performed, after radium treatment: 74 cases were treated in this way; the operability-rate was 35 per cent. The lymphatic glands were involved in 21 per cent; seven of the cases were in cervices left after subtotal hysterectomy. Operation is advised four or five weeks after radium treatment.

TRICHOMONAS VAGINALIS AS A CAUSE OF PRURITUS VULVAE.

It is suggested that infection might arise from the anus, but this was thought to be unlikely since no trichomonas could be cultivated from the faeces of infected patients.

It was found that after drying pus for three hours the trichomonads would again become actively mobile when mixed with warm normal saline.

No trichomonads could be obtained from the urethras of the partners of infected women, and in only one woman could the trichomonad be obtained from the urethra. It appears that the infection might readily arise from lavatory seats.

A method of staining which is a modification of Gram's stain is described. Attempts were made to cultivate the trichomonads but after some time they appeared to be overwhelmed by the growth of bacteria. Finally a culture medium containing folliculin and acriflavine at a low concentration, to inhibit the bacterial growth, was used with excellent results.

The symptoms and the methods of treatment are described. The author finds the most successful method is to clean the vagina with a 1 in 1,000 solution of hexylresorcinal and insert four gelatine capsules containing sodium bicarbonate into the vaginal fornices. A similar powder is blown over the vaginal walls and vulva. This treatment is given every day for a week and then on alternate days for another week. If the trouble recurs after the next menstrual period the patient is treated for another week and throughout the following menstrual period.

W. R. Winterton.

The American Journal of Obstetrics and Gynecology.

Vol. 32, No. 4.

President's address. B. P. Watson.

Anaemia in pregnancy. F. L. Adair, W. J. Dieckmann, and K. Grant.

*A further study of extraperitoneal pelvic conditions in women. L. Brady.

The relation of the endocrine system to the growth of tumours. L. A. Emge and Kathleen M. Murphy.

Oestrogenic substances in the blood of women. C. F. Fluhmann.

Total versus subtotal hysterectomy. J. R. Goodall.

Total hysterectomy by the abdominal route versus the vaginal route in benign uterine disease. E. H Richardson.

Retroperitoneal pelvic tumours encountered by the gynaecologist. J. R. Miller.

Radium irradiaton for benign haemorrhage. C. C. Norris and C. A. Behney.

*The relation of endometrial hyperplasia to adenocarcinoma of the uterus. Emil Novak and Enmei Yui.

Secondary sequelae after interposition of the uterus. W. T. Dannreuther.

*Immediate repair of cervical injuries. W. C. Danforth.

The relation of acanthosis nigricans to abdominal malignant disease. J. C. Masson and H. Montgomery.

A Further Study of Extraperitoneal Pelvic Conditions in Women.

In this paper Brady begins by stressing the importance of an accurate diagnosis of extraperitoneal and intraperitoneal conditions, especially when dealing with inflammatory masses in the pelvis, because the general and surgical treatment in the two groups is so essentially different. Abscesses, the result of parametrial infection, are the extraperitoneal pelvic lesions which most frequently call for surgical interference, and the author reports his experience of 53 cases since 1900. In 50 of these cases the infection was located in the broad ligaments and in three it developed in the connective tissue in front of the cervix. In the former group the suppuration was bilateral in four cases and in the latter group pus pointed in the connective tissue of the anterior abdominal wall in two cases and in one case directly under the bladder. An investigation of the aetiological factors revealed that in 18 cases infection followed abortion, in 18 it followed normal full-time delivery, in 11 it followed instrumental or operative delivery, in 1 the removal of a dermoid cyst, in 1 acute vulvitis, and in 4 cases no aetiological cause could be found.

Most of the patients were ill on admission and all complained of lower abdominal pain. In 41 of the 53 cases an abdominal mass was found, and in 3 of the 53 cases nothing abnormal was palpable on pelvic examination.

The author points out that in the great majority of cases the diagnosis is easily made from the history and physical examination, but when the characteristic findings are absent the extraperitoneal nature of the lesion may be missed. In 6 cases of his series this occurred and the peritoneal cavity was opened. While discussing the operative treatment of these inflammatory collections in the broad ligament Brady emphasizes the risk of drainage through the vagina by an incision in the posterior fornix. The pushing of a pair of artery forceps upwards and outwards to strike the pus is very likely to puncture the indurated peritoneum or injure the uterine artery or ureter. He strongly advises the inguinal incision and extraperitoneal drainage of the inflammatory mass. He maintains that the drainage is more complete and the average stay in hospital is considerably shortened by this operation, especially when it is performed before a mass is palpable above Poupart's ligament. He also comes to the conclusion that it is not wise for another pregnancy to follow the evacuation too quickly; two patients, who conceived six weeks after discharge from hospital, aborted and developed severe sepsis; one of them died.

The author completes his paper with a consideration of other rarer extraperitoneal lesions, such as myomata and cysts, and discusses the various theories of their origin.

The Relation of Endometrial Hyperplasia to Adenocarcinoma of the Uterus.

Novak and Yui quote the opinion of various authors about the relation between hyperplasia and the future development of adenocarcinoma, and the assertion of most of them that they have never seen the two conditions present together in the same case. After studying their own cases these authors have gradually come to the conclusion that hyperplasia is not so devoid of harmful possibilities as was at one time thought. More and

more frequently are they finding border-line pictures, the co-existence of hyperplasia and carcinoma, and cases of functional hyperplasia which later develop carcinoma; this has made them consider more seriously a possible relation between the two.

They go on to describe how the epithelium of the lymphatic glands may show a definite metaplastic change so that it perfectly resembles the epithelium of the Fallopian tubes. In other cases they say that the glands themselves may show a marked increase in number with practically no interglandular tissue and with atypical convolutions and involutions. Such findings, especially when associated with epithelial overactivity, have been described as early carcinoma. In only 13 cases of the reproductive epoch (1.3 per cent of the total series) did the author find such proliferative activity as to raise the question of possible malignancy; none of the patients developed carcinoma at a later date. They think that these and other changes are probably brought about by an excess of oestrin, as comparable findings have been obtained experimentally in rats. They also describe a squamous metaplasia which may involve either the surface epithelium or that of the glands. The theory that this transformation is a later development in an adenocarcinoma is supported by one of their cases in which a most remarkable instance of this change was found.

The most surprising development in this study was the finding of an apparently typical and active hyperplasia in 40 women long after the menopause. They point out that the finding of hyperplasia in such women lessens the value of this as a sign of the presence of a granulosa-celled ovarian tumour. Since in 19 of these cases, in which the abdomen was opened, the ovaries were found to be senile, the authors think that some other structure, probably the pituitary gland, takes over the formation of oestrin after the menopause.

During their study of 104 cases of actual adenocarcinoma they found a high percentage (20.03 per cent) in which there was a co-existing hyperplasia of the endometrium. In 40 of these cases sections through non-cancerous endometrium were not available and so the percentage in the remaining 64 cases reaches 39.06. In 11 other patients the uterus had been curetted at the menopause or there was a history of menopausal flooding. Therefore the authors came to the conclusion that there must be a definite relation between cancer and this post-menopausal hyperplasia. As the only known cause of such hyperplasia is the presence of a persisting excess of oestrin, the authors also feel that an abnormally long-continued subjection of the endometrium to the stimulation by oestrin may be the predisposing factor in the formation of cancer.

Immediate Repair of Cervical Injuries.

Danforth advocates the immediate repair of cervical injuries of childbirth. From his experience over a number of years he is of the opinion that the idea that the tissue is so soft that the stitches tear out does not hold as he has had satisfactory results in more than three-fourths of his cases.

He also shows figures that the other objection of sepsis cannot be brought forward as an argument against immediate repair. He stresses the importance of careful and accurate suture and that this can only be done if the

operator realizes that after laceration the muscular portion of the cervix retracts. Thus the cross section of the torn edge forms a V, the two arms of the V being the mucosa of the cervical canal and the vaginal surface of the cervix respectively. He points out that the sutures must go sufficiently deep to grasp the retracted muscle.

Bryan Jeaffreson.

The Journal of the American Medical Association

Vol. cviii, No. 18, May 1st, 1937.

Familial congenital heart disease. David B. Snelling.

Vol. cviii, No. 20, May 15th, 1937.

*Obstetric amnesia, analgesia and anaesthesia: their relation to sudden death in labour. Thaddeus B. Montgomery.

Pirquet cubicles for infants. Bela Schick.

Vol. cviii, No. 21, May 22nd, 1937.

Pregnancy complicating subacute bacterial endocarditis. Joseph Felsen, Henry Schumer and A. G. Osofsky.

The reproductive performance. (Editorial).

Vol. cviii, No. 22, May 29th, 1937.

*Sulphanilamide in gonococcal infections. John E. Dees and J. A. C. Colston.

*Sulphanilamide and prontosil in haemolytic streptococcal infections. R. R. Mellon, Paul Cross and F. B. Cooper.

A combination resuscitator and incubator for newborn infants. (Clinical Notes).

Metabolism in pregnancy. (Editorial).

Vol. cviii, No. 23, June 5th, 1937.

*Intra-uterine respiratory movements of the human foetus. F. F. Snyder and Morris Rosenfeld.

Rhythm of human fertility. (Editorial).

Vol. cviii, No. 24, June 12th, 1937.

The incidence of trichomonads in the vagina, mouth and rectum: evidence that vaginal trichomonads do not originate in the mouth or intestine. P. Brooke Bland and A. E. Rakoff.

*Biopsy studies of the human endometrium: criteria of dating and information about amenorrhoea, menorrhagia and the time of ovulation. John Rock and Marshall K. Bartlett.

Vol. cviii, No. 25, June 19th, 1937.

*The treatment of heart disease complicating pregnancy. H. J. Stander and Katherine Kuder.

Breast milk and lyzozyme. (Editorial).

Intra-uterine foetal respiration. (Current Comment).

Vol. cvix, No. 1, July 3rd, 1937.

Roentgenographical diagnosis and anatomical studies of a quintuple pregnancy. E. C. Hamblen, R. D. Baker, and G. D. Derieux.
The development of acute haemolytic anaemia during the administration of sulphanilamide. A. M. Harvey and C. A. Janeway.
Impending gangrene due to ergotamine tartrate. (Clinical Notes).

OBSTETRIC AMNESIA, ANALGESIA AND ANAESTHESIA: THEIR RELATION TO SUDDEN DEATH IN LABOUR.

From an analysis of the maternal deaths in Philadelphia over a 5-year period it was found that there was an improvemnt in obstetric practice except that which had to do with the intra-partum period. It is the aim of the author to show what relation the more general use of analgesic drugs has to this increase. The main thesis is that full obstetric analgesia or amnesia cannot be obtained without an increase in the maternal mortality. Of the methods commonly employed it would seem that spinal anaesthesia has the highest maternal mortality, with the barbiturates coming second. A method which proved satisfactory to the author was the use of morphine-scopolamine analgesia combined with infiltration of the perineum with procaine hydrochloride, which was productive of a small loss of blood, a rapid third stage and a lively infant in all cases.

SULPHANILAMIDE AND PRONTOSIL IN HAEMOLYTIC STREPTOCOCCAL INFECTIONS.

Experiments were made with streptococcal strains of different virulence on mice and guinea-pigs. It was found that if large doses of maximal virulence were given, the treated animals merely survived longer than the controls. but when the initial streptococcal inoculation was reduced 90 per cent recovered, as against 100 per cent which died in the control series. It is important to administer the sulphanilamide or prontosil at the earliest possible moment in all cases. The authors believe that phagocytosis plays no part in the action of these drugs, and found no qualitative changes in the character of the histological response to the haemolytic streptococcus as a result of the administration of the drugs.

INTRA-UTERINE RESPIRATORY MOVEMENTS OF THE HUMAN FOETUS.

It can be shown that rabbit embryos perform intra-uterine respiratory movements, by injecting indian ink into the amniotic cavity, and, after birth, demonstrating the stain in the alveoli. If foetal respiratory movements have been inhibited by the previous injection of pentobarbital sodium, no such staining will appear. The authors believe that similar respiratory movements occur in the human foetus, and by motion pictures claim to have recorded the foetal respiratory movements, which can readily be distinguished from maternal respirations and from transmitted pulsations from the aorta. Again, the presence of amniotic fluid and debris in the foetal lungs is considered a normal occurrence; such debris may produce

obstruction or infection. Asphyxia neonatorum should be regarded as a suppression of a previous activity rather than as the failure of some new mechanism to begin functioning at birth. The foetal respiratory centre before birth is known to have a peculiar sensitivity to anoxaemia and narcosis, and the avoidance of these factors immediately before birth is of greater importance than later efforts at resuscitation.

BIOPSY STUDIES OF HUMAN ENDOMETRIUM: CRITERIA OF DATING AND INFORMATION ABOUT AMENORRHOEA, MENORRHAGIA AND THE TIME OF OVULATION.

This paper deals with the findings on microscopical examination of endometrium removed in 457 biopsies. The instrument employed was the suction curette, which the authors preferred because it removes the superficial layers only, and can generally be used without anaesthesia.

Nothing new is advanced in regard to the physiology of the menstrual cycle, but the photographic illustrations of the endometrium at various stages of the cycle are excellent.

THE TREATMENT OF HEART DISEASE COMPLICATING PREGNANCY.

This paper is based on the case-histories of 563 hospital discharges of obstetric patients suffering from cardiac disease from the Lying-in Hospital, New York. The incidence of cardiac disease among the patients discharged during the period under review was 3.97 per cent, and the maternal mortality in the cardiac patients was 7.1 per 1,000 as compared with a general mortality of 2.8 per 1,000. Mitral stenosis, alone or complicated by other lesions, accounted for over 80 per cent of the cardiac cases treated.

The authors believe that the cardiac output in normal pregnancy begins to increase about the fourth month of gestation, from which time there is a steady increase until term is reached. After delivery there is a return to normal, reaching the non-pregnant level about 4 weeks after labour. The total increase in cardiac output, expressed in minute-volume, is about 50 per cent. In grading the cardiac cases the well-known grouping of the cases into the four categories advocated by the New York Heart Association is followed. It was found that over half the patients fell into the least serious category (Group 1), and that only 14 per cent came into the two most advanced grades.

It is advocated that pregnant patients suffering from the two earlier grades of cardiac disease should be admitted to hospital two weeks before term for enforced rest, and that delivery should be spontaneous or assisted with the forceps, depending on the degree of decompensation present. In more advanced cases earlier admission to hospital is indicated, and there is a higher incidence of assisted delivery. Caesarean section with sterilization is advocated for patients in Group 4 in whom therapeutic abortion has been considered unnecessary.

In the series under review the infantile mortality was not in excess of that for all women confined.

F. H. Finlaison.

Surgery, Gynecology and Obstetrics.

Vol. lxv, No. 1, July 1937.

*Analgesia, anaesthesia and the newborn infant. S. H. Clifford and F. C. Irving.

*Pseudomenstruation in the human female. C. Mazer and S. L. Israel.

Vol. lxi, No. 2, August 1937.

*The early recognition and treatment of cervical cancer. E. Novak.

*Hydatidiform mole and chorion-epithelioma; a 5-year study. A. Mathieu.

*An 8-year survey of Caesarean sections at the William H. Coleman Hospital. F. W. Gustafson.

Analgesia, Anaesthesia and the Newborn Infant

Clifford and Irving, making a study of analgesia and anaesthesia and their effect on the newborn, have found that opium derivatives administered during labour have an unfavourable influence, proportionate to the amount given and the time interval between the administration of the drug and the birth of the child.

In this group 57 per cent of the infants required some stimulation before they would breathe and cry normally and 25 per cent were asphyxiated to the point of requiring artificial resuscitation. Successful maternal amnesia was obtained in 34 per cent of cases.

The barbiturates have had no painful effect upon either the life of the foetus or the life of the newborn infant.

Over 10,000 mothers received sodium amytal or pentobarbital in the first 5 years and in this interval the stillbirth-rate and neonatal death-rate have fallen below the level of the preceding 5 years.

Pseudomenstruation in the Human Female.

Cyclic uterine bleeding, clinically indistinguishable from normal menstruation from an endometrium totally lacking in the usual secretory changes, occurs in 30 per cent of sterile women who present no abnormality.

The condition is rarely encountered in fertile or potentially fertile women, and may be due to a failure of ovulation, or to developmental or acquired lack of response of the uterus to a normal ovarian activity, or to a quantitative or qualitative disharmony between the two ovarian hormones, oestrin and progestin.

When the diagnosis is based on endometrial findings alone the term "pseudomenstruation" is preferable to "anovular menstruation" because the presence of the latter cannot be proved without concomitant study of the ovaries.

The Early Recognition and Treatment of Cervical Cancer.

Apart from individual and collective efforts in educating women as to the early signs of cancer, the chief contribution the general practitioner can make to the cancer campaign is the intensive study of the cervices which he has to examine. In such studies he must not only look for the obvious cancer picture, but he should search carefully for the early lesions

and those which are merely suspicious, and in these he should press for accurate diagnostic differentiation, which will generally mean biopsy and microscopic examination.

Although it is comparatively easy for the gynaecologist and pathologist to differentiate the benign from the malignant, in a certain group of cases it may be difficult. This group is becoming larger in many clinics because of the present-day interest in such lesions as leucoplakia, believed by some to be an important precursor of cancer.

In such intensive studies on the cervix the colposcope and the Schiller test, both of which are discussed at length in this paper, are of great value, though both have many limitations, and neither would seem to be suited for general use among practitioners.

The treatment of cervical cancer is briefly discussed. The prevailing popularity of radiotherapy is fully justified by the fact that it gives final results just as good as those of expert surgery, with much lower primary mortality and morbidity rates. In a small group of cases, however, surgery, often combined with post-operative radiotherapy, is still a rational procedure, and in this group are especially to be placed early cases of a radioresistant type, in which the patient is a good operative risk and the surgeon is well trained in the technique of the radical operation.

HYDATIDIFORM MOLE AND CHORION-EPITHELIOMA; A FIVE-YEAR STUDY.

An effort has been made to analyze the records of all cases of hydatidiform mole and chorion-epithelioma which have occurred on the Pacific Coast in the years 1931 to 1936.

There are 127 cases of hydatidiform mole reported in this study, and over 80 per cent occurred in the first half of pregnancy. Only 1 patient had had a previous hydatidiform mole. Bleeding was the outstanding symptom. Vesicles were found in 18 patients, painful contractions were present in 28, and 27 had excessive nausea and vomiting. There are three reported cases in which a foetus was present with a hydatidiform mole.

In considering the use of the Aschheim-Zondek test the author expresses surprise that it was not used more frequently. In 71 cases the test was either not done or not recorded. Of the remaining 56 cases the test was made during the molar pregnancy in 28 cases and in the other 28 the test was made subsequently to treatment. In the first group, in which the test was done during the molar pregnancy, it became negative in 11 cases after curettage, in 8 after hysterectomy, in 2 after passage of the mole, in 1 after vaginal hysterectomy, and in 1 after normal spontaneous delivery of an infant weighing six pounds (hydatidiform changes were found in the placenta). In the other group, in which the test was done subsequently to treatment negative results were obtained in 14 cases after curettage, 6 after hysterectomy, 2 after passage of the mole, and 1 after vaginal hysterectomy. In 2 instances the test was positive after curettage and a further test was not done.

The author feels that one can rightly conclude that as long as there is living chorionic tissue present, the Aschheim-Zondek test will be positive and if none is present it will be negative.

In this study 28 cases of chorion-epithelioma are reported, 15 followed moles, 7 followed pregnancy or abortion, 5 existed with a mole, and 1

occurred coincidentally with pregnancy. The symptoms were identical with those of the mole and diagnosis was made clinically and with the aid of the Aschheim-Zondek test in 9 cases, from curettings in 15, and after hysterectomy in 4. Every case in which the Aschheim-Zondek test was used gave a positive result. In treating these patients 24 hysterectomies were done, 14 total and 10 supravaginal. Three patients were treated by dilatation of the cervix and curettage of the uterus. One had a vaginal implantation removed.

Practically 80 per cent of the chorion-epitheliomata were found within 20 days after the passage of the mole in those cases in which the patients had been properly examined, in which sufficient Aschheim-Zondek tests had been done and in which pathological specimens were examined. This fact has led the author to believe that certain cases of mole have the potentiality of malignancy.

AN EIGHT-YEAR SURVEY OF CAESAREAN SECTIONS AT THE WILLIAM H. COLEMAN HOSPITAL.

The greatest single factor in the reduction of the mortality from Caesarean section at the Coleman Hospital has been the wider adoption of low cervical Caesarean section. The author believes this is safer than the classical operation not only in cases of trial labour but also in elective cases. A study has been made of all the Caesarean sections at the Coleman Hospital performed during the period 1927 to 1936, and on this the author has based his conclusions. He believes that the transverse incision with the Phaneuf technique is a very satisfactory procedure in the lower uterine segment. He states that if low cervical operations were substituted for the classical operation, in America, the mortality-rate would be halved.

C. D. Read.

Bruxelles Médical.

Vol. xvii, No. 27, May 2nd, 1937.

*Endometrioma. Mm. Rocmans and Petitfrère.

Vol. xvii, No. 28, May 9th, 1937.

A case of congenital absence of the cranial vault with recovery. G. Robyn.

Société Clinique des Hôpitaux de Bruxelles: report of the meeting held on April 10th, 1937.

A case of strangulated pyosalpinx in a ventral hernial sac. Mm. Abbeloos and Pohl.

Vol. xvii, No. 30, May 23rd, 1937.

*Atmocausis in the treatment of uterine haemorrhage due to metropathia haemorrhagica. J. A. Schockaert.

Vol. xvii, No. 31, May 30th, 1937.

*A case of genital actinomycosis in the female. J. A. Schockaert and E. de Cooman.

The value of the Bordet-Wassermann reaction during pregnancy and the puerperium. Dr. Straetmans.

Vol. xvii, No. 33, June 13th, 1937.

*Prolonged retention of foetal bony fragments in the uterus. R. Bourg and P. Lahaye.

Société Belge de Gynécologie et d'Obstetrique. Report of the meeting held on May 1st, 1937.

(*a*) Congenital absence of left half of the diaphragm in the newborn. J. Snoeck.

(*b*) The complcations of induced abortion. R. Karhausen.

Vol. xvii, No. 34, June 20th, 1937.

*Myomectomy followed by pregnancy. J. Rouffart-Marin.

Société Belge de Gynécologie et d'Obstetrique. Report of meeting held June 5th, 1937.

(*a*) Indications and methods for inducing abortion in pregnancy complicated by tuberculosis. A. Brindeau.

(*b*) Feminine sterility and the *p*H of cervical secretion. J. A. Schockaert and G. Delrue.

Vol. xvii, No. 35, June 27th, 1937.

*Intravenous injections of alcohol in pelvic infective thrombophlebitis. G. Lambert.

Vol. xvii, No. 36, July 4th, 1937.

Two cases of congenital polycystic disease of the kidneys in the newborn. G. Legrand

ENDOMETRIA.

Emphasizing that the diagnosis of endometrioma is not made sufficiently often, the author describes 2 cases. In the first the tumour was a chocolate cyst in the right broad ligament. It was not connected with the Fallopian tube, uterus or peritoneum, and probably arose from a developmental inclusion of the Müllerian duct. In the second case the growth was situated in the rectovaginal septum of a nulliparous woman, aged 23 years. The diagnosis was made at laparotomy but firm adhesions to the rectum made excision of the endometrioma impossible. Subsequently small cysts appeared in the vaginal vault. This patient was treated successfully by the insertion into the growth of 20 mgm. of radium for 4 hours.

In addition to the theories of origin, the various surgical and radiological methods of treatment are discussed. The author points out the advantages of using small doses of radium for surgically inaccessible growths in young patients in whom it is desirable to conserve ovarian function.

Atmocausis in the Treatment of Uterine Haemorrhage due to Metropathia Haemorrhagica.

The severe haemorrhage associated with metropathia haemorrhagica may be treated by means of drugs, hormones, X-rays, radium, curettage, or hysterectomy. In young patients it is undesirable to destroy ovarian function and the more conservative measures sometimes fail to cure. In such cases control of symptoms by the intra-uterine application of superheated steam is useful treatment.

This type of therapy was introduced at the end of the nineteenth century but suffered from technical difficulties. A new instrument is described; in this the steam is produced by means of an electrical resistance immersed in in water. The current is reduced when a temperature of 120°C. is reached. Although it is stated that anaesthesia is not necessary, the author used sodium evipan in his cases and always excluded malignant disease by preliminary curettage. The steam passes into the uterus by way of an ebonite cannula of which several sizes are available.

The details of 45 cases are recorded. The duration of treatment varied from ½ to 4½ minutes. Amenorrhoea of only short duration follows when steam is injected for ½ to 1½ minutes. If permanent amenorrhoea is desired exposures of 4 to 4½ minutes are advised. Thirty-eight patients were cured and 5 improved.

There were no post-operative complications and no cases of subsequent cervical stenosis.

On four occasions the uterus was removed following atmocausis and the histological changes are described. After an exposure of 4 minutes necrosis occurs to the depth of only 2 mm., but after the elapse of some months the endometrium is completely replaced by fibrous tissue. In the case of shorter exposures some endometrial tissue survives.

This form of treatment is contra-indicated by the presence of old or recent pelvic infection, fibromyomata, products of conception and previous uterine operations such as Caesarean section or myomectomy.

A Case of Genital Actinomycosis in the Female.

A patient, aged 35 years, had been ill for 10 months when first seen by the writer. She complained of paroxysms of lower abdominal pain, general weakness, pyrexia and amenorrhoea. Posterior colpotomy had previously been performed but was not followed by clinical improvement.

After blood transfusion, laparotomy was performed. The uterus, appendages, bladder and intestines formed a fixed mass in the lower abdomen. After separation of adhesions, bilateral pyosalpinges and a right ovarian abscess were found. Total hysterectomy with removal of both appendages was carried out after hemisection of the uterus. Some thick yellow pus escaped during the operation. After actinomycosis had been diagnosed by section, potassium iodide was administered by mouth.

The patient made a good recovery but 6 weeks after operation developed a swelling in the abdominal wall. Incision into this revealed no pus. Subsequent treatment with diathermy had good results, and 1 year after the original operation the patient was well except for induration of the abdominal wall and two fistulae.

Sections of all tissues showed characteristic lesions and organisms.

There are two types of genital actinomycosis, primary, which is rare, and secondary, of which this case is an example. The author considers that the organisms probably reached the appendages from the intestinal tract. The symptoms and signs presented by this patient are typical of the condition but the diagnosis can rarely be made except by laparotomy. In addition to excision, deep X-ray therapy is recommended.

Prolonged Retention of Foetal Bony Fragments in the Uterus.

Two cases are recorded in which small bony fragments remained in the uterus after abortion. The fragments were retained for 6 months and 3 years, respectively. In each case the patient had intractable discharge and irregular uterine haemorrhage. The cervicitis was first treated in both cases, but the symptoms were only cured when the portions of bone were removed by curettage. The osseous fragments were so small that they were partially embedded in the endometrium and were not, therefore, spontaneously expelled.

The authors believe that this condition is more common than the literature would indicate, and that bony fragments give rise to endometritis, cellulitis, and salpingitis.

Myomectomy Followed by Pregnancy.

A sterile woman, aged 33 years, was found to have a retroverted uterus containing multiple fibromyomata. Ten tumours were removed and the uterus suspended in an anteverted position. Conception occurred within 6 months. The author considers that myomectomy is more dangerous than hysterectomy.

Intravenous Injections of Alcohol in Pelvic Infective Thrombophlebitis.

Alcohol, administered by mouth, has long been used in the treatment of infective conditions, but it was first given intravenously in 1927. Alcohol is quickly and completely diffused through all the tissues. Four cases of puerperal thrombophlebitis were treated by the injection of 200 c.c. of 35 per cent alcohol, in saline, every two days. One patient was desperately ill with metastatic abscesses: all recovered.

The mode of action of alcohol is discussed, and the writer believes that its efficacy is due to the facts that it is a rich source of energy and conserves body proteins, and that it directly inhibits growth of bacteria.

During its administration the patient experiences a feeling of warmth in the limb and, after a short period of excitement, falls into a deep sleep. Although the injected vein always becomes thrombosed, the treatment has no other ill-effect. The hepatic and renal functions are not disturbed.

T. N. A. Jeffcoate.

Revista Italiana di Ginecologia.

Bologna.

Vol. xx, February 1937.

*Congenital diaphragmatic hernia. Chimeuti.

*Cancer of the cervix and vagina in young women. Puccioni.

Chemical reaction of the smooth muscle of the human Fallopian tube. Morosi.

Urethral motor activity during pregnancy. Cordaro.

Congenital Diaphragmatic Hernia.

Chimeuti describes 4 cases of foetal congenital diaphragmatic hernia. The infants died immediately, or less than half an hour after birth. The livers of all the infants were considerably enlarged and most of the abdominal organs were pressed up into the thorax. In 3 cases pregnancy was complicated by hydramnios. In 2 mothers the Wassermann reaction was strongly positive and there was a history of syphilis.

Chimeuti discusses the effect of (*a*) hydramnios in the dislocation of the intestine into the thorax (in 3 cases this involved the large intestine including the caecum, the appendix, the ascending colon and the transverse colon), (*b*) the cause of the hepatic enlargement and of the aplasia of the lungs. Such malformations are obviously incompatible with life, and, in spite of attempted artificial respiration, death occurs from asphyxia, since, with the establishment of a negative inspiratory pressure, dislocation of the abdominal viscera into the thorax increases.

Some cases of survival for several years have been described. Troland describes one case in which the patient lived to 55 years.

Cancer of Cervix and Vagina in Young Women.

Puccioni describes in detail 20 out of 125 cases of cervical and vaginal cancer in young women under his care. His conclusions are that (1) Cancer of this type in young women formed about 16 per cent of his total cases. This is a higher percentage than that given by most authors. (2) In most cases pregnancy had preceded the development of cancer. Three young women of 20 were contemporaneously pregnant. (3) The type of cancer varied; sometimes it was ulcerative; sometimes diffuse or mixed. In 2 cases the growth was an adenocarcinoma; in 18 it was squamous-celled in type; in 1 of these mature keratinization was observed, in 12 keratinization was semi-mature, and in 5 it was immature. (4) The percentage of operability was higher than at a later age. (5) The results of therapy were satisfactory. The survival was longer than that of older patients. The best results were obtained with surgical treatment combined with pre-operative or post-operative radiotherapy. (6) From estimation of the pathological reports, the clinical course and the therapeutic results, he does not think that the degree of malignancy and the severity of the clinical symptoms were greater than in women of more advanced age.

J. H. Filshill.

Zentralblatt für Gynäkologie.

No. 20, May 15th, 1937.

*The significance of hormonal disturbance in the production of cystic mammary disease and cervical epithelial metaplasia. L. Herold and G. Effkemann.

*The action of prolonged and increasing follicular hormonal treatment upon the vaginal epithelium of different animals. L. Herold and G. Effkemann.

Short wave therapy of pre-eclampsia and eclampsia. J. Emmrich.

*A case of pregnancy with an intra-uterine pessary in position. K. Thomsen.

A new diagnostic symptom to differentiate between inflammatory and non-inflammatory genital tumours, especially tumours on the left side and retro-uterine tumours. E. Schleyer.

The complement fixation reaction in the diagnosis of gonorrhoea in the female. A. Klamartsik.

No. 21, May 22nd, 1937.

Mortality following implantation of the ureter into the bowel after Coffey. F. v. Mikulicz-Radecki and C. Krauspe.

A combination of the ischio-bulbo-cavernosus plastic operation with a wide levator plastic operation. W. Stoeckel.

Absence of the left kidney accompanying absence of the left adnexa. H. Huber.

Malformations of the urinary and genital organs. Bl. Szendi.

No. 22, May 29th, 1937.

Obituary of Otto von Franque. H. Martius and W. Stoeckel.

The administration of uterine stimulants. E. Holzbach.

The topographical classification of uterine pain in normal and pathological labour. S. Lorand.

Topographical data for the recognition of the pains of labour in uterus subseptus and uterus bicornis. S. Lorand.

Yesterday *summum jus*, to-day *summa injuria*. F. Meder.

*A case of primary echinococcal cyst of the uterus. A. Missirloglou and N. Anagnostidis.

No. 23, June 5th, 1937.

The results to the present time of intravaginal radiation for uterine carcinoma. F. Erichsen.

An investigation into the menstrual cycle at the menopause. W. Breipohl.

Anencephaly: the intra-uterine diagnosis. H. Kückens.

An attempt at the establishment of the relation between the intercristal diameter and the transverse diameter of the normal pelvis. K. Brost.

The radiological examination of the spine and pelvis in tuberculosis and carcinoma and its application in gynaecology and obstetrics. H. Hellendall.

No. 24, June 12th, 1937.

*The clinical course and therapy of carcinoma of the external genitalia. (1) Report on the clinical course and treatment of carcinoma of the vulva. A. Göbel and A. Hamann.

*Follicular hormone in milk fistulae and mastitis. S. Ernst.

*Swelling of the mammary glands caused by hormonal action before puberty. E. Preissecker.

Placenta zonaria humana completa. K. H. Kiefer.

Chorea gravidarum and its treatment. F. Drazancie.

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Obituary of Josef Halban. R. Köhler.

*Studies in ovarian function and its excitation in uniovular twins. K. Tietze and R. Grützner.

Complete ossification of a cephalhaematoma in an infant with resulting permanent deformity of the skull. B. Ottow.

The advantages of blunt dissection of the lower uterine segment *in situ*. W. Hauser.

Dorso-superior transverse lie. G. Kaboth.

*Dermoid growths in the vagina. Fr. Härle.

Balneological therapy and gynaecological treatment. W. Engelmann.

No. 26, June 26th, 1937.

Unilateral adnexal defect, its occurrence and clinical signs. P. Caffier.

Two sections through a scar resulting from removal of the appendix. P. Strassmann.

Carcinoma of the stump after supravaginal amputation of the uterus. G. Stark.

Of what value is the regulated injection of eunarcon in operative midwifery and gynaecology. K. Zinram.

The mathematical localization of points in the true pelvis by means of the "winkelstaben." R. Knebel.

The human placenta as a producer of the so-called anterior pituitary hormone. I. Kido.

No. 27, July 3rd, 1937.

Rapid vaginal delivery after Delmas. H. R. Schmidt Elmendorff.

Uterus bicornis unicollis and abortion. P. Caffier.

A case of habitual abortion with uterus bicornis and ligamentum rectovesicale. K. Hübscher.

Uterine cysts and their origin. K. Fukushima and M. Saito.

Cervical cysts as obstructions to delivery. H. Kraatz.

Practical findings of the conception theory of Knaus-Ogino. E. Rumpf.

No. 28, July 10th, 1937.

Cure of carcinoma of the uterine body by curetting. A. Mayer.

Our results of the treatment of cervical carcinoma with radium. J. C. Ahumada, O. Prestini, and J. del Togno.

Further cases of primary carcinoma of the portio and later carcinoma of the breast. H. Hellendall.

The significance of weight less than normal in the origin of intracranial birth injury. T. Brander.

Perforation of the small intestine by a stercolith followed by peritonitis as a cause of death in the newborn. H. Kraatz.

THE SIGNIFICANCE OF HORMONAL DISTURBANCE IN THE PRODUCTION OF CYSTIC MAMMARY DISEASE AND CERVICAL EPITHELIAL MATAPLASIA.

Herold and Effkemann consider that tumour formation is influenced by the presence of follicular hormone. There is not, however, a generalized disposition to tumour formation but rather a tendency to localize activity at sites which are liable to undergo localized regenerative changes. If there is a general tendency to tumour formation then the follicular hormone may set up a precancerous condition.

The writers have carried out a histological examination of the uterine body and cervix and of the mammary glands in animals which had been treated with follicular hormone. In a considerable percentage of cases so treated they found changes in these organs which could definitely be classed as precancerous.

THE ACTION OF PROLONGED AND INCREASING FOLLICULAR HORMONAL TREATMENT UPON THE VAGINAL EPITHELIUM OF DIFFERENT ANIMALS.

Herold and Effkemann treated a series of animals over a period of 2 to 3 months with increasing doses of follicular hormone. For this purpose they treated mature whole female rats, mature castrated female rats, and immature female rats, as well as mature castrated and mature whole female mice.

After this course of treatment they found in each case that there was a high degree of keratinization of the vaginal epithelium with the production of marked root formation into the underlying tissues.

A CASE OF PREGNANCY WITH AN INTRA-UTERINE PESSARY IN POSITION.

Thomsen describes the specimen removed at operation from a woman whose uterine prolapse was treated by hysterectomy and colporrhaphy. This woman had had six pregnancies all going to full time except the last which ended at the thirty-sixth week, eight months before the operation. All her labours and puerperia were entirely uneventful, her only trouble being an increasing uterine descent after each pregnancy.

The removed uterus contained a spiral metal pessary, lying just above the internal os, which was partially buried in the muscular uterine wall. The total length of the pessary was 9 cm.; it was made of silver. The upper end was buried to a depth of 1.5 to 2 cm. and the lower end to a depth of 0.5 cm. in the wall of the uterus.

After the finding of this intra-uterine pessary the patient stated that nine months before she had had it inserted by her family doctor but that within one month of its insertion she again became pregnant. She therefore asked her doctor to remove it but, as he could not find it, it was thought to have dropped out.

A Case of Primary Echinococcal Cyst of the Uterus.

Missirloglou and Anagnostidis record the case of a woman of 35 years of age from Smyrna who came to them for treatment of menorrhagia of two years' standing.

Laparotomy was performed to investigate a cystic pelvic tumour. On opening the abdomen the cyst was found to be in the uterine wall and under the belief that it was a myoma which had undergone cystic degeneration the uterus was amputated above the vagina.

On examination of the specimen the cyst was found to contain a clear fluid filled with hooklets; but daughter cysts were not found. There was no sign of any other cystic disease in the abdomen.

The writers suppose that the echinococcus gained access to the uterus by way of the vagina and they consider that there must have been a marked change in the *p*H of the vaginal secretion to allow of the solution of the cyst's capsule.

Report on the Clinical Course and Treatment of Carcinoma of the Vulva.

Göbel and Hamann review a series of cases which have come under their treatment during the years 1915 to 1936. They have considered their cases, 69 in all, from the points of view of frequency, age of onset, localization, clinical manifestations, direction of spread and histology. Their methods of treatment were divided under the headings of:

(*a*) *Surgical treatment,* implying diathermy of the vulval tumour and extirpation of the inguinal glands.

(*b*) *Radiation with X-rays, or radium,* implying either prophylactic, post-operative or frank radiation of the glandular region; or radium or X-ray treatment of the vulva.

The results of treatment were given separately for those cases of a duration longer than 5 years and those with one of less than 5 years. The resulting cases of cure over a period of 5 years were 26.3 per cent as against a perscentage of cure published in the literature of 24.3 per cent.

Follicular Hormone in Milk Fistulae and Mastitis.

Ernst refers to the report of Lindemann in 1936 on the rapid resolution of a case of milk fistula following a severe case of mastitis.

The writer has recently had under his care two patients in whom repeated incision and counter drainage of multiple mammary abscesses resulted in the formation of milk fistulae which could not be induced to close when treated by the usual orthodox methods. These were finally treated with injections of 50,000 units of progynon B oleosum and the daily administration by mouth of 1,090 m.e. of menformonfolliculin in tablets.

Within two days the mammary fistula dried up and began to heal; neither patient experienced any further trouble.

Swelling of the Mammary Glands caused by Hormonal Action before Puberty.

Preissecker refers to the occurrence of painful mammary nodules in the

breasts of young girls from the age of 9 to 12 years before the onset of puberty. This mammary hypertrophy appears to result from the action of ovarian hormones; the follicular hormone induces cystic changes in the breast and the corpus luteum hormone an epithelial hyperplasia of the glandular tissue.

He refers to the changes which occurred in a woman of 36 years of age with defective ovarian secretion. She began to menstruate at 20 years of age and afterwards only at intervals of 4 to 6 months. She was examined and found to have a very small uterus and small palpable ovaries. After 4 months of amenorrhoea she was given a course of injections of progynon B oleosum for three months; she received a total dosage of 550,000 units. She then bled *per vaginam* for 14 days; this loss was followed by a regular loss for 6 days at intervals of 26 days.

Two months after the last injection the patient noticed a swelling in the breast which gradually increased in size from that of a bean to that of a cherry; it was tender on pressure. The swelling was excised and found to possess a cystic glandular structure.

Studies in Ovarian Function and its Excitation in Uniovular Twins.

Tietze and Grützner have carried out an investigation into the menstrual histories of 23 pairs of uniovular twins. They first had their interest directed towards this investigation by the casual remark of a patient that she was expecting the onset of her menstrual period because her twin sister had started overnight.

After giving detailed case-histories of all the twins the writers came to the following conclusions:

	No.	Synchronous	Nearly concordant	Discordant
Onset ...	23	10 difference up to 1 month	6 difference 2 to 3 months	7 difference over 3 months
Tempo ...	23	18	2 occasional	3 always
Duration ...	23	20 regular	2 ,,	1 ,,
Strength ...	23	19 ,,	3 ,,	1 ,,
Pain ...	22	21 ,,	—	—
Climax ...	3	3 ,,	—	—
Arrhythmia causeless	5	3 ,,	—	2

The writers consider that there is a definite similarity in the menstrual cycle in uniovular twins.

Dermoid Growths in the Vagina.

Härle records the case of a patient who was admitted to hospital during the last month of her pregnancy because of severe uterine haemorrhage.

The patient was a twin; she had previously had three deliveries at term and three abortions. She had septicaemia after one of the abortions and was in bed for 10 weeks with repeated rigors.

On examination after admission to hospital she was found to be bleeding freely from the uterus and two hard nodular swellings were felt in the vagina. The vaginal nodules were excised and the uterus was evacuated by vaginal Caesarean section.

The nodules were examined histologically and found to be dermoid tumours containing sebum, hair and teeth. The only abnormality found when the patient was examined at the end of the puerperium was a small scar on the right vaginal fornix, which appeared to be continuous with an area of thickening in the right parametrium.

The writer suggests that the patient had a dermoid tumour in the right ovary which became infected after the septic abortion, the abscess so formed later pointed into the vagina and left some of the constituents of the tumour in this position.

R. H. B. Adamson.

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*Spontaneous and artificial rupture of the membranes during labour. Anton Sunde.

*Spontaneous and artificial rupture of the membranes during labour. S. E. Wichmann.

*Experimental investigations into the function of the pituitary isthmus in the production of gonadotropic hormones of the anterior pituitary gland. A. Westman and D. Jacobsohn.

The pernicious forms of pregnancy anaemia. Hans-Ludwig Kottmeier.

Leukaemia in pregnancy. E. Brandstrup.

Carcinoma of the vaginal stump after supravaginal amputation. Michael Nielsen.

SPONTANEOUS AND ARTIFICIAL RUPTURE OF THE MEMBRANES DURING LABOUR.

Sunde reviews a series of 937 cases of labour and classifies them according to the time of the rupture of the membranes. The term "primary rupture" is applied to rupture of the membranes before the onset of the pains of labour; and "ordinary rupture" to the escape of liquor amnii when the size of the os uteri is not known.

When an examination of the os is made at the time the membranes rupture the terms (1) *anticipated*, (2) *physiological*, and (3) *retarded* are used, according to whether the membranes rupture before, during or after dilatation of the os. He finds that primary rupture occurred in 13 per cent of the cases in his series; primary rupture is more common in primigravidae than in multiparae and increases in frequency with advancing age. The mean duration of labour is shorter in cases of primary rupture, which he attributes to *travail insensible*. He finds that the risk of infection after primary rupture is greater than after ordinary rupture.

The maternal mortality was 0.96 per cent and the foetal mortality 1.1 per cent.

Spontaneous and Artificial Rupture of the Membranes During Labour.

Wichmann, of Helsinski, reviews a series of 2,557 cases of primiparous labour and 716 cases of second labour with spontaneous rupture of the membranes. The ages of the patients were between 20 and 24 years. In addition there was a second series of cases comprising 1,307 primiparae and 1,046 multiparae in whom the membranes were unruptured or ruptured on examination; and a third series comprising 416 primiparae and 330 multiparae of different ages in whom the membranes were artificially ruptured.

The more important results of these investigations were:—

(1) Premature rupture occurred equally commonly in primiparae and multiparae, being present in 10 to 12 per cent of patients between the ages of 20 to 24 years. Advancing age increased the tendency to premature rupture.

(2) Premature rupture of the membranes definitely shortened the duration of the first stage of labour, probably as a result of non-painful contractions during the time of latency.

(3) While artificial rupture of the membranes appears to be followed by a shortening of the duration of labour the writer does not recommend its use for this object but only for cases in which the onset of labour at a definite time must be obtained, the shorter duration being an incident.

(4) When internal examinations are made only by experts under the most careful aseptic conditions the risk of infection is not increased with the duration of labour after rupture of the membranes.

(5) The morbidity and mortality of mothers and infants were not increased by early rupture of the membranes.

Experimental Investigation into the Function of the Pituitary Isthmus in the Production of Gonadotropic Hormones of the Anterior Pituitary Gland.

Westman and Jacobsohn have carried out a series of experiments on rats and rabbits by severance of the pituitary stalk, with the following results: (1) After severance of the stalk the ovaries atrophy and gradually reach the same condition as after hypophysectomy, although the pituitary body presents no change in the rat and the rabbit. (2) Cauterization of the stalk immediately after copulation is followed by failure of rupture of the follicle and corpus luteum formation in the rabbit. (3) Cauterization of the stalk longer than two hours after copulation is followed by corpus luteum formation with a shorter duration of function. (4) Ovulation does not follow copulation shortly after cauterization of the stalk. (5) Ovulation does not follow electric stimulation of the cerebrum immediately following the cauterization of the stalk. In control animals this is regularly followed by ovulation. (6) After cauterization of the stalk the granulosa cells of the intact follicles do not degenerate as is the case after hypophysectomy in the rabbit. This last experiment shows that the gonadotropic pituitary hormones are not transferred from the hypophysis by way of the pituitary stalk to the cerebrum but are indirectly secreted into the general circulation. All the experiments show that nervous impulses which are transferred to the hypophysis from the cerebrum by way of the pituitary stalk have a decisive effect on the production of gonadotropic hormone by the pituitary.

R. H. B. Adamson.

Arquivo de Patologia

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*Chorio-epithelial formations in the ovaries of guinea-pigs. Athias.

*The presence and significance of cell nests in basal-celled carcinoma. Prates.

Chorio-epithelial Formations in the Ovaries of Guinea-pigs.

The subject of this article is some curious formations discovered by Loeb, in 1905, in the ovaries of young guinea-pigs, which he called *chorio-epithelial* or *chorio-placental*. They are complex cells in which are seen elements of clearly embryonic origin and mononuclear or polynuclear giant cells with irregular nuclei. Often these cells follow the blood-vessels, invading their walls and provoking haemorrhage. They also penetrate into the follicles and into the corpora lutea. These formations, which appear to be small transitory tumours, are derived, according to Loeb and other authors, from the intra-ovarian division of atretic follicles of De Graaf. Courrier, Oberling, and other investigators describe cases similar to those of the American author.

In his present work, Athias describes 4 cases he has recently observed in virgin guinea-pigs from 2 to 4 months old which had always been isolated from males. He never found the formations in adult animals, in which Loeb, Courrier and Oberling say they have sometimes seen them.

Illustrations of histological preparations accompany Athias's article, and show well how interesting the Loeb formations are. He agrees with Loeb that they are important in relation to the origin of embryos, and in a later work he hopes to give more details and describe 2 cases of a typical tumour found in the ovaries of guinea-pigs.

The fact which is of chief importance to remember is that the parthenogenetic development of the oöcyte in the ovary may give origin, especially in young females, to more or less typical embryonic formations and sometimes to complex chorio-placental bodies all representing small transitory tumours. Fecundation in the ovary cannot be invoked as an explanation, since in Loeb's cases, as in the author's, the animals had always been isolated.

The Presence and Significance of Cell Nests in Basal-celled Carcinoma.

Prates gives a historic account of certain cutaneous tumours first described by Braun in 1892 which he named endotheliomata, because he thought they differed from cancerous tumours both clinically and histologically.

Krompecher holds that Braun's endotheliomata are not true endotheliomata, but carcinomata which resemble them macroscopically and microscopically. He named them baso-cellular carcinomata. The views of

subsequent investigators regarding the general classification of malignant cutaneous neoplasms are very much at variance, but they all agree that these basal-celled carcinomata show a very feeble tendency to keratinization. Prates, however, has found absolutely typical specimens showing cell nests. Now, as squamous-celled carcinoma, of which keratinization is a marked feature, are more malignant than others, he has found it interesting to study the behaviour of keratinizing basal-celled carcinoma.

By means of statistics he disproves Koerbel's belief that the cell nests were formed as a result of X-ray treatment, which at the same time increased the malignancy. He has ascertained that in several carcinomata with cell nests before treatment not one could be detected after. He thinks that after treatment by radium the prognosis can be founded neither on the type of tumour-cell, nor its colour reaction. What does count, according to Prates, in basal-celled carcinomata is their localization. Thus on mucosa all types are equally malignant. As regards skin, basal-celled carcinomata with cell nests are not more malignant than those without them.

J. H. Filshill.

REPORTS OF SOCIETIES

THE NORTH OF ENGLAND OBSTETRICAL AND GYNAECOLOGICAL SOCIETY.

JUNE.

A meeting of the Society was held in Newcastle-upon-Tyne on Friday, June 11th, 1937.

Dr. WILLIAM HUNTER (Newcastle) read papers on

TWO CASES OF RUPTURED UTERUS.
TWO CASES OF PROLAPSED CORD.

Case 1. E.M. The patient was admitted to hospital as a case of failed forceps on the second child of twins; the first and macerated twin had been delivered by a midwife seven hours previously. An injection of posterior pituitary extract had been given by the doctor in attendance before the patient left home. At previous confinements a stillborn foetus had been normally delivered and a living child instrumentally.

The patient was suffering from shock, and complained of severe abdominal pain. The child appeared to be presenting by the vertex; the head was deeply engaged in the pelvis. The foetal heart was not heard.

The vagina was extensively bruised and lacerated, but the cervix was normal and fully dilated. The foetal head was found to have passed through a large transverse tear in the posterior fornix into the pouch of Douglas. An unsuccessful attempt was made to deliver the foetal head into the vagina with a view to applying the forceps, after which the general anaesthetic was discontinued.

Upper segment Caesarean section was performed under local anaesthesia with novocaine, the foetal head being displaced from the pouch of Douglas into the uterine cavity with some difficulty, and a stillborn child weighing 7 pounds was extracted. Three transverse tears, each admitting three fingers, and several smaller lacerations, were found in the posterior uterine and vaginal walls opening into the pouch of Douglas.

Subtotal hysterectomy was performed, during which gross damage to the bladder or rectum could not be demonstrated. The wound was sutured, and a gauze pack was passed from the cervical stump through the laceration in the posterior fornix into the vagina.

During the latter part of the operation 12 ounces of glucose-gum solution were infused into a vein; this was followed, after direct matching, by transfusion of 12 ounces of citrated blood of group IV. Routine nursing treatment was carried out after the operation and a definite improvement took place in the patient's condition. This improvement was maintained until the

following night, when she collapsed, after passing urine, from which time a progressive deterioration took place, and she died five hours later, 26 hours after the operation, from acute streptococcal peritonitis.

Case 2. R.T., a primipara, aged 32 years, was brought into hospital from the district, where she had been in labour for 10 hours, because the uterine contractions were inefficient and the foetal head remained high.

She was in good general health, the vertex was presenting with the head above the pelvic brim, and the foetal heart was heard. Uterine contractions were infrequent and poor. Vaginal examination showed the vaginal orifice to be narrow, the cervix two fingers dilated, the membranes intact, and the presenting part high. A minor degree of flat pelvis was discovered, the true conjugate diameter measuring 3¾ inches; the pelvic cavity was roomy. Labour progressed very slowly; various sedatives and oestrin were given. The membranes ruptured spontaneously 58 hours, and the os became fully dilated 82 hours, after the onset of labour. At the latter time, on examination under anaesthesia, it was found that the vaginal wall was slightly oedematous, the vertex lay in the transverse diameter of the middle of the pelvic cavity, and a large caput succedaneum was present. Under ether anaesthesia, an L-shaped medial episiotomy was performed, as the forceps blade would not pass through the narrow ostium vaginae, and the head was manually rotated into the antero-posterior diameter of the pelvic cavity with a view to applying the forceps. On applying the left blade a resistance to its complete introduction was encountered when the tip reached the level of the child's neck. Further investigation revealed the presence of a contraction ring. Under deep anaesthesia aided by an intramuscular injection of 5 c.c. of 50 per cent magnesium sulphate with 5 minims of 1–1,000 adrenalin hydrochloride, the contraction ring relaxed, and the head was displaced into the upper uterine segment. The ring again contracted to a certain degree, but the hand was introduced into the uterus and a foetal foot was grasped as a preliminary to the performance of internal version. The cord was felt to be collapsed and pulsating feebly. When the fist was clenched on the foot, the contraction ring was felt to recede from the operator's wrist, and the operation was therefore postponed until the cause of this had been ascertained. The uterine wall was palpated before the hand was withdrawn, and an extensive vertical rent was found posteriorly. This was packed with sterile gauze, the episiotomy incision was sutured, and preparations were made for immediate abdominal operation. The patient was now suffering from collapse and shock of increasing severity. The abdominal cavity was opened under nitrous oxide and oxygen anaesthesia, and the peritoneal sac was found to contain free blood. A stillborn foetus, 7 pounds in weight, was delivered by upper segment Caesarean section and the tear in the posterior uterine wall was investigated. As this proved to be so extensive that repair was considered to be impracticable, the placenta was removed and subtotal hysterectomy was performed. This operation was rendered unusually difficult by the extreme friability of the tissues related to the lower uterine segment. Artery forceps cut, rather than compressed, the tissues, and even the clamp put on the left uterine artery completely divided the vessels and tissue, while sutures cut out from the cervical stump. Gauze packs were left in position to check troublesome oozing, and the abdomen was closed.

Routine treatment was given for shock and collapse, and this evoked a satisfactory response. From this time convalescence was nonpyrexial and uneventful. The gauze was removed from the wound on the fourth day; a fortnight later the wound was firmly healed and the cervical stump was similar to that found after subtotal hysterectomy for gynaecological disease. The patient returned home during the third week in a satisfactory condition.

Csae 3. L.B. This patient had had 9 previous confinements, in 8 of which the child had been delivered by the breech. During the present pregnancy she had attended an antenatal clinic where external cephalic version had been attempted or performed on several occasions to convert a shoulder presentation into a vertex presentation.

On admission, in labour at term, the lie was oblique with the breech lying in the right iliac fossa, the cervix was two fingers dilated, and the membranes ruptured.

External cephalic version was tried, but the attempt proved unsuccessful as the head could not be dislodged from the fundus of the uterus. The breech was therefore displaced over the pelvic brim.

Three hours later the breech appeared at the vaginal orifice during pains, and after a further 1¾ hours breech delivery was commenced. Under light anaesthesia, traction with the fingers in the groin until the legs could be disengaged from the perineum, and with the aid of pressure on the fundus by an assistant the child was delivered as far as the thorax. The umbilical cord was taut, and the usual loop of cord could not be drawn down. Progress was arrested before the shoulders were born, and an elastic resistance to the descent of the head was felt. The presence of a contraction ring was suspected, and both arms were brought down as a preliminary to a more detailed investigation. On introducing the hand into the uterus alongside the chest wall, no contraction ring was found, but the cord was coiled several times around the neck and the taut placental end could be felt passing up by the side of the head. As it appeared that the cord was anchoring the foetus to the uterus, the trunk was drawn as far down as possible, the funis was divided between clamps and unwound from the neck. Delivery was now completed with ease by the Mauriceau-Smellie-Veit method. The child was born in a state of asphyxia livida; it responded to routine treatment; the perineum was intact, and the third stage of labour was normal. The puerperium was uneventful and the baby thrived at the breast while in hospital.

Case 4. L.H., a primigravida, aged 24 years, was first seen in labour at her home by a student, who found a loop of pulsating umbilical cord protruding from the vulva and lying in the bed. The patient stated that labour had commenced at term and the waters had broken an hour ago, after which the string had come down. A foetal head was felt in the left iliac fossa, and a transverse lie was diagnosed.

The patient was put in the knee-chest position, the cord was wrapped in gauze and a message was sent to the Resident Medical Officer. On arrival, he found about 12 inches of cord prolapsed through a thick cervix which would admit only two fingers with difficulty. Manual reposition was unsuccessfully attempted, and the patient was transferred to hospital. After a rapid abdominal examination an oblique lie with the foetal head lying in the left iliac fossa was diagnosed. *Per vaginam* the presenting part was

found to be high, and, on introducing the finger through the cervix, only small parts could be reached. As the foetal head could not be displaced from the left iliac fossa, no further attempt was made to replace the cord, which was washed with spirit and returned to the vagina. Upper segment Caesarean section was performed, and a living child of 5 pounds 12 ounces was delivered in a state of asphyxia livida, from which it soon recovered. This child had presented by the breech in the left sacro-anterior position; the prolapsed cord was attached to this child. The placenta occupied an anterior position in the uterus. After extraction of this child, the uterus remained bulky, and, on introducing the hand into its cavity, another amniotic sac containing a second foetus was discovered. The membranes were torn and another child of 5 pounds 4 ounces, which cried immediately after birth, was delivered. It had presented by the vertex in the left occipito-posterior position, and its head had apparently rested in the left iliac fossa. The second placenta was attached to the posterior uterine wall. The operation was completed without further incident.

Convalescence was normal apart from some post-operative intestinal distension, which was relieved by an enema. The first child, whose cord had been prolapsed for four hours, thrived at the breast, but the second, artificially fed, showed progressive deterioration and ultimately died on the fourteenth day.

Discussion.

Mr. J. E. Stacey (Sheffield), in discussing Dr. Hunter's cases, referred to three cases of ruptured uterus he had seen recently. In his experience multiparity predisposed to rupture, and he was interested to learn that one of Dr. Hunter's patients had been a primigravida. In his three cases the uterus ruptured during the first stage; in each case rupture was due to a contraction ring, and he thought the latter a more common cause of ruptured uterus than was generally recognized.

Professor E. Farquhar Murray (Newcastle) said he had no particular faith in anaesthesia causing relaxation of contraction rings. He thought Caesarean section was good treatment in such cases.

Professor William Gough (Leeds) asked Dr. Hunter whether he had considered lower segment Caesarean section for his case.

Dr. Hunter, in reply, said he thought adrenalin was helpful in causing temporary relaxation of a contraction ring. He had considered lower segment Caesarean section, but the patient was very ill, and the lower segment very oedematous.

Mr. C. Walsh (Liverpool) read a paper on

A Case of Sudden Death.

Dr. Walsh said that sudden death occurring during the course of gynaecological or obstetrical operations was, fortunately, very rare. Its occurrence was a tragedy for the relatives, very disturbing to the peace of mind of the operator, and involved medico-legal deliberations.

The tragedy was more intense when it occurred during some simple

gynaecological test or operation which was usually regarded as devoid of risk to life.

Mrs. B., aged 41 years, was referred to the gynaecological clinic of the Mill Road Infirmary by her doctor for sterility. She was anxious to be treated at this clinic, because a friend of hers who had attended and been treated for sterility had conceived within two months.

Her doctor had tested her husband for potency and found active and normal spermatozoa in a condom specimen. She stated that she had been married 13 years and had always menstruated regularly and without pain; and her cycle was one of 3 or 4 days every 28 days. Her last menstrual period began on February 12th, 1937.

She denied ever having any vaginal discharge, and had always been in good health.

Ten years previously she had sought gynaecological advice for her sterility and was treated in another hospital in Liverpool when, apparently, a posterior section of the cervix was performed.

On examination the vulva and vagina were normal. There was a hare-lip-like condition of the cervix due to the previous operation, but no evidence of erosion or cervicitis. The body of the uterus felt normal in position, size and mobility, and the appendages felt normal. There was no apparent pelvic abnormality. Her general condition was healthy, and clinically all other systems were normal.

Dr. Walsh suggested that she should come into the hospital for Rubin's test. She readily agreed to this, but her husband at first refused to sign permission for an anaesthetic. Later he acceded to his wife's wishes.

On March 15th, 1937, one day prior to her expected menstrual period, she was anaesthetized with ethyl chloride followed by open ether through a Halton's mask.

The uterus was of normal length; a uterine sound easily passed through the internal os. An intra-uterine catheter passed easily and without the slightest resistance. Connecting up the tubing to the insufflator, a pressure of 150 mm. Hg. was first tried. Air could be heard passing through the Fallopian tubes by listening over the lower abdomen. On repeating the test three times up to a pressure of 200 mm. Hg., three observers heard the hissing sound usually associated with the passage of air through Fallopian tubes into the peritoneal cavity. The total volume of air used was 150 c.c.

Satisfied that the tubes were patent, Dr. Walsh withdrew the catheter and noticed that a very slight trickle of blood issued from the os. The anaesthetist announced that the patient was in a poor condition.

She suddenly became cyanosed and respiration stopped, although the heart was beating rapidly but feebly. She gave two deep gasps and died within four minutes despite cardiac stimulants and artificial respiration.

The coroner was notified and he requested a post-mortem examination. This was performed 22 hours later by Dr. Hewer. The uterus and adnexa were uniformly congested as in the immediate premenstrual condition. Both ovaries were normal, the right having a recently ruptured corpus luteum. The Fallopian tubes were congested, free from adhesions and patent. On squeezing the tubes a bead of thick material was expressed; examination of this later showed it to contain endothelial cells and a very few

organisms, but no pus cells. This was presumably material blown up from the uterine mucosa. The endometrium was microscopically intact without evidence of trauma due to the insertion of the cannula. Section of the uterus confirmed the diagnosis of the endometrium's being in the immediate premenstrual or menstrual stage. The uterine veins were full of air, and bubbles of air could be seen in the mesosalpinx. The inferior vena cava was ballooned with air and contained very little blood. The right auricle was devoid of blood and contained only air bubbles. All the other organs were healthy. Death was due to air embolism. It must be presumed that air passed into a patent venule in the premenstrual endometrium, but it is difficult to understand why the main volume of air did not follow the path of least resistance through the patent Fallopian tubes.

Dr. Walsh said he had looked up the literature of the condition. Rubin did not appear to have had a fatal case of air embolism; but Louis Bonnet stated that two cases of air embolism had been reported by Rubin. Bonnet described two cases—one in a patient of 42 years of age suffering from cardio-renal disease, and in which he suggested that the pressure was too light and volume of air used too large; the other occurred in a patient with fibromyomata and bilateral pyosalpinges, in which again the pressure and quantity of air used were excessive.

Moench reported two cases. In one case at post-mortem the right heart contained numerous gas bubbles and air was also present in the inferior vena cava and right femoral vein. The Fallopian tubes were closed. The other case was rather more complicated and suggested that shock rather than air embolism was the cause of death. The best discussion of this tragic condition was by Mansfield and Dudits who suggested that the entry of air was facilitated in this case by reason of unrecognized tuberculous endometritis and that too much air entered the blood. The Fallopian tubes were occluded.

They concluded from experimental evidence that the cause of death in air embolism was the occlusion of the coronary arteries.

Dr. Walsh said that in future he would take warning from this case and observe the following points in technique: (1) To use a minimal pressure. (2) To limit the volume of air. (3) Never to perform insufflation too near to the expected or completed menstrual period.

Discussion.

Professor E. Farquhar Murray (Newcastle) said that he had heard of an exactly similar case, and he thought great care was necessary in doing the operation.

Professor William Gough (Leeds) asked why such a large pressure should be used.

Mr. St. George Wilson (Liverpool) showed an X-ray film demonstrating a case in which lipiodol had been used to see whether the Fallopian tubes were occluded, after an operation for sterilization. The shadows in the film showed that lipiodol was in the veins as well as in the uterus. A film taken next day showed that the lipiodol had disappeared from the veins.

Dr. Hunter (Newcastle) thought that insufflation should only be carried out 2 or 3 days after menstruation.

Dr. WALSH, in reply, said that he now remembered a case in which he had attributed death to the anaesthetic, whereas it was really due to an air embolus.

Dr. K. V. BAILEY (Manchester) read

A FURTHER NOTE ON THE OPERATION OF OVARIAN EXTROVERSION.

Dr. Bailey said he had delayed setting down his conclusions with regard to the results of this series of cases until now—that was a period of 16 months since he first read his communication to the North of England Obstetric and Gynaecological Society in February 1936. He had done so because at that time the two points raised in the discussion were (1) the advisability of carrying out laparotomy for a condition which was not a surgical necessity, and (2) the lack of proof of ovulation following operation even in the successful cases.

To-day he was in a better position to answer these questions as the result of observation of the effects of continued endocrine treatment of the most modern type in this class of case, and as the result of the occurrence of pregnancy in one of the cases of his series.

Dr. Bailey again briefly outlined the technique of his operation. Laparotomy was performed, and a wedge, having its base at the periphery, was excised sagitally from the cystic ovary. The apex of the wedge was carried down to the region of the hilum. Sutures were then passed through the ovary in such a way as to turn the cut edges of the ovary partially inside out.

Regular menstruation was successfully established immediately after operation in 13 cases of this series; there were 4 failures. There were 4 cases which were treated by modern endocrine therapy, as advocated by Kaufmann, both stimulatory and substitutional in type, prior to operation with no permanent result. He regarded these as control cases. Endocrine substance in some form was administered orally in nearly all of the cases, and in 9 cases antuitrin S. was given by injection with oestroform by the mouth. He quite agreed with Kaufmann's views that this amount of treatment would of itself be of no avail.

In this series, therefore, there were patients who were now menstruating regularly every 4 or 5 weeks with a normal loss, who were previously suffering from either persistent relative amenorrhoea of 3 to 6 months duration, or definite secondary amenorrhoea varying from 1 to 3 years duration. These patients at the time of operation were suffering from other symptoms in addition to the amenorrhoea complained of. Some had lost a considerable amount of weight through worry and anxiety coupled with the underlying endocrine disturbance, others had gained in weight just as definitely, although he found these were in the minority; loss in weight was associated with the grossly retrogressive change in conjunction with chronic cirrhosis of the ovaries. In others the weight remained unaltered, but in nearly all there was a definite underlying nervous upset, and in some, symptoms bordering upon neurasthenia. He understood that these patients regarded themselves as different from other women. The

question of marriage and pregnancy obsessed some. A few of the patients who had kept the knowledge of this abnormal function to themselves were heading for a nervous breakdown as the result. In the married patients the continued presumption of pregnancy with disillusion had its nervous effect. He regarded patients with the condition of prolonged relative amenorrhoea or developed secondary amenorrhoea as, in the main, physically ill from nervous upset, however well some of them might control it.

This method had been widely adopted since Kaufmann first propounded his treatment by the injection of endocrine substances, and most observers would agree that only temporary results were likely to follow treatment. Replacement therapy was not likely to reinstitute regular menstruation after prolonged relative, or developed secondary, amenorrhoea had been established. Moreover, the cost of such therapy was as yet largely prohibitive.

In assessing the value of hormone therapy as applied to secondary and relative amenorrhoea Dr. Bailey quoted Bishop, who in the *British Medical Journal* of April 1937, said: "The results of hormone therapy in this group of cases are disappointing. Permanent re-establishment of the menses occurs in 10 to 20 per cent of cases of secondary amenorrhoea, and in cases of oligomenorrhoea and hypomenorrhoea regularity and normal loss are achieved and maintained in 30 to 40 per cent. Replacement therapy is only temporary in its effect. Discontinue the administration of oestrin in a case of ovarian deficiency and the uterine muscle will atrophy. Stimulation therapy yields comparatively poor results. Re-establishment of menstrual rhythm in a long standing case of amenorrhoea demands readjustment of a delicate endocrine balance whereby the ovary is subjected to hormonal stimuli of varying nature and intensity throughout the cycle."

Dr. Bailey said that, to his mind, these words were the crux of the situation, in an understanding of the difficulty or impossibility even of adjusting this balance by mechanical means alone, in the presence of ovaries which were physiologically inert.

He mentioned these points because he believed that endocrine therapy of this type should be tried in all cases to begin with because it was non-operative, and in spite of the unscientific optimism which had replaced the unreasonable scepticism with regard to this treatment during the last five years. In those cases, however, in which it gave no permanent result, and in which the gross lesions of the ovaries, already referred to, could be estimated by examination, in conjunction with prolonged relative amenorrhoea or secondary amenorrhoea, he believed that this operation of extroversion of the ovaries should be carried out, provided the patient fully realized that a successful result could not be guaranteed.

He considered that the associated physical and nervous upsets of the present, not to mention the restricted functional outlook for the future, of which the patient was well aware, was sufficient indication for the performance of laparotomy for this condition in these days of relatively safe surgery. In his opinion it represented a mistaken view to look upon this condition as one which was not immediately threatening the life of the patient, and, therefore, one which did not call for every effort for its relief. Such a view took no note of the years ahead which only the patient, herself, had to face handicapped by a developing neurosis. Nor

can the view that if many of these cases were left alone they would right themselves be of much solace to the patient in whom a trial by endocrine therapy had not produced regular menstruation. It was well known that in certain cases menstruation had re-established itself without assistance after a period of amenorrhoea. He particularly referred, however, to those cases of consistent relative amenorrhoea, showing as they did an inadequate endocrine function extending over a long period, and to developed secondary amenorrhoea of a duration of a year or more. In these cases, if cystic degeneration of the ovaries could be clinically diagnosed, there could be little doubt that the pathological lesion present was progressive and that the prospect of the return of normal function was remote.

The technique of this operation was based upon the impossibility of deeply situated Graafian follicles, which were as yet unaffected by the degenerative changes in the ovary, to reach the surface and rupture thereon. Facilities for this phenomenon were the result of making a new, wide and free ovarian surface. The regularity with which menstruation had followed operation in the majority of these cases strongly suggested ovulation from ovaries which certainly showed no recent or remote evidence of this at operation. Proof of this fact, however, was not forthcoming in this series until recently by his Case 3. The patient had had amenorrhoea for 2¼ years; there was no trace of a corpus luteum in either ovary at operation. She became pregnant 7½ months ago. This pregnancy had continued normally until the present time. Injections of 2 clinical units of proluton 3 times weekly had been given from the fourth week to the twelfth week with the object of preventing abortion. In this case regular menstruation occurred 5 weeks after operation and continued at regular intervals of 4 to 5 weeks for 2 years, until the onset of the present pregnancy without endocrine assistance. In this case, therefore, ovulation had certainly taken place recently and it was, therefore, fair to assume that ovulation had occurred on other occasions since the operation. Some regular stimulus to the production of menstruation had been present in this case as in the other successful cases of this series, which was not present before operation. In his opinion this stimulus was the phenomenon of ovulation which could not, of course, be proved in any case unless conception took place. It was remarkable that this particular patient was once exhibiting the long period of secondary amenorrhoea of 2 years' duration—a fact which must go far to disprove any likelihood of ovulation and normal menstrual rhythm recurring spontaneously without interference. He therefore suggested, that in these cases in which regular menstruation had recurred shortly after operation and had continued practically without endocrine assistance, that the close association in time between the onset of regular menstruation and operation pointed directly to the production of a continued menstrual stimulus due to the latter, and that this stimulus was the reproduction of ovulation which alone could maintain the continuance of menstrual rhythm.

Whilst recognizing, therefore, the inadvisability of subjecting young subjects suffering from developed relative, or secondary, amenorrhoea to laparotomy without a thorough trial of treatment on general and endocrine lines over a length of time, he would definitely assert that in those cases in which this treatment *failed* a lesion of the ovaries, such as had been

described, could be clinically detected. such a lesion would obviously become more pronounced as time went on, thus rendering the outlook less and less favourable. In cases in which time itself failed to rectify menstrual function, and particularly when this failed to improve as time went on, and in cases in which the nervous system showed signs of derogatory affection in consequence of the fact of amenorrhoea, this operation of extroversion of the ovaries was one which was justifiable on the foregoing grounds, both with the object of the restoration of normal menstruation and improvement for the prospect of pregnancy, provided the patient and responsible relatives understood that a result so far as the former was concerned could be expected in approximately 75 per cent of cases.

Discussion.

The President (Dr. Bride) said that Dr. Bailey had cleared up many points which were not clear in his previous communication.

Mr. Harvey Evers (Newcastle) said that in his experience cystic ovaries were rare in secondary amenorrhoea. He mentioned a case in which a whole year of endocrine therapy was necessary to produce a menstrual period. The patient became pregnant almost immediately, and a year after the first confinement she had another baby.

Dr. J. W. A. Hunter (Manchester) congratulated Dr. Bailey. He thought it disappointing that a surgical method should give a better result than endocrine treatment. He asked whether the amenorrhoea in Dr. Bailey's cases was due to pituitary or to ovarian deficiency. He could not see how an ovarian operation could affect a pituitary deficiency. He asked whether any of Dr. Bailey's cases had developed dysmenorrhoea? And whether the basal metabolic rate had been estimated. He thought it would be useful if such cases could be thoroughly investigated before and after the operation.

Dr. Bailey, in reply to the President, said that the risk of the operation was small, with little bleeding at the time. It was his invariable practice subsequently to investigate for adhesions. In reply to Mr. Evers he said that in his series he could, in most cases, feel cystic ovaries. In reply to Dr. J. W. A. Hunter he said that the basal metabolic rate had not been estimated and endometrium had not been examined, because all but two of the cases in this series occurred before the publication of Kaufmann's paper on the endocrine treatment of this condition. In his opinion most cases of secondary amenorrhoea were due to primary ovarian deficiency or insensitivity of the ovaries or uterus to pituitary stimulus. He agreed with Dr. Hunter about the indiscriminate use of this operation. That was why he had been 16 months considering his cases before reading his second paper. He said it should not be done except as a last resort.

Dr. Bryan Williams read a paper on

The Use of Protonsil in Obstetrics.

Dr. Williams said that the group of substances to which we might refer by the name of "protonsil" had now been in general use in this country

for about a year, and, as the claims made about the results obtained from them might be said to be revolutionary, their use could not be too fully reported. Although their value in medicine and surgery might be enormous if these claims were upheld, their value in obstetrics promised to be even greater; the original work in this country and much of the subsequent work had been done in this direction. He had now used these drugs at Walton Hospital since shortly after the appearance of the original article by Colebrook and Kenny in June 1936, and he had thought it worth while to report the results he had obtained in obstetrics. No doubt many members would wish to discuss this subject and to report their own experiences; he would, therefore, briefly report his results with a short comment.

He had used them both for the treatment of cases of established puerperal or post-abortum infection, and also in an attempt at the prophylaxis of puerperal sepsis; he would describe the findings separately.

Treatment. The drugs used had been the protonsil soluble drug of Messrs. Bayer, and the protonsil album preparation of sulphonamide, part of which had been generously supplied by the makers. In the early stages the protonsil red tablets were used, but these were soon discontinued in favour of the protonsil album. It had now been shown that the protonsil soluble form had its bactericidal effect only in the body when it had changed into the sulphonamide. It had also been shown that this substance acts very quickly when taken by mouth. In future, no doubt, the oral route would be the main route of administration, and had already supplanted the parenteral route at Queen Charlotte's Hospital. The latter route still had some advantages, for example, when a patient with peritonitis was vomiting, and could not swallow large numbers of tablets, which had rather a bitter taste.

In a few of the early cases the protonsil soluble was given intravenously, but subsequently it had been given intramuscularly. It was absorbed very quickly, as shown by the speedy appearance in the urine of a deep red colour.

The substance itself was quite painless on injection, but the bulk of the fluid when big doses were used was very painful in a patient who was wasted by severe sepsis, and was not tolerated well by patients in the querulous condition often associated with sepsis. Most patients had received it by mouth and by injection. The average dose by injection had been 136 c.c., usually in doses of 20 c.c.; by mouth 132 tablets, or 44 grains. The biggest dose given in one day had been 100 c.c. Toxic effects had been extremely rare in cases treated with it, as opposed to those in which it had been given prophylactically, and only one case of cyanosis had been noted. Renal irritation had not been observed, although catheter specimens had not been taken as a routine at the end of treatment.

The results. Up to date protonsil had been used in 53 cases which had been treated to a conclusion. In 23 of these a haemolytic streptococcus was not isolated, and these cases were not to be considered in detail. In 8 cases the injection was localized to the uterus; in 4 it involved the pelvic peritoneum or the Fallopian tubes; in 8 others it was extra-pelvic. There were 3 deaths, in none of which was a post-mortem examination obtained. One was a case of ulcerative endocarditis following delivery, superimposed

upon an old mitral stenosis, in which a non-haemolytic streptococcus was isolated from the blood-stream. These cases were notoriously resistant to every form of treatment, but it was interestng to note that the treatment brought down the temperature, and this was also found in another case of non-pelvic origin in the hospital at the same time. The second death occurred during the puerperium in a case of lobar pneumonia complicated by erysipelas without evidence of pelvic sepsis. The third was apparently a case of pelvic abscess and thrombophlebitis in which no streptococci were obtained in spite of repeated cultures. It was possible that the infection was due to an anaerobic streptococcus.

Dr. Williams did not think any evidence could be drawn from these figures as to the effect of protonsil on infections not due to a haemolytic streptococcus, though some experimental evidence had been brought forward showing their value in this direction.

The 30 cases in which a haemolytic streptococcus was obtained would now be considered. A few cases in which a haemolytic streptococcus was found were excluded: in these, the infection was so mild that the temperature was normal by the time the bacteriological report was obtained. One case of pelvic abscess was included in which culture of the organisms was not attempted, but the films showed streptococci and the case had the clinical appearances of infection due to a haemolytic streptococcus.

A classification similar to that adopted by Colebrook and Kenny had been used. There were 13 cases in which the infection was limited to the perineum, vagina, or uterus, 7 in which the pelvic peritoneum, cellular tissue, veins, Fallopian tubes, or ovaries were involved; and 10 cases of septicaemia, or general peritonitis, or both.

Group 1. Two cases followed abortion, and 7 full-time labour. In one case a staphylococcus aureus was found in a culture of the blood, but as it was found only in one culture-tube after several days' incubation, it had been thought better to look upon it as a contaminant.

There were no cases in which any extension of the infection or suppuration occurred during treatment, except in one case in which signs suggesting salpingitis appeared, but subsided. In one case phlebitis of the leg developed. Otherwise no complications developed, and there were no deaths.

Group 2. In this group there were 4 cases of cellulitis, 1 of pelvic peritonitis, 1 of pelvic abscess, and 1 of thrombophlebitis. In all of these the infection was established when the treatment was commenced. In 2 drainage was carried out by the vaginal route. In all the others the localized inflammation subsided, and there were no fatal cases.

Group 3. This included 10 cases of septicaemia, or general peritonitis, or both. All these were admitted as emergency cases with an established infection. In 3 of the cases there was evidence of a focus of infection in the neighbourhood of the patient at the time of delivery, although this was proved bacteriologically in only 1 case, in which the organism proved to be of a similar type to that isolated from another patient who died from peritonitis. In 8 cases a positive blood-culture was obtained. In 1 of the other 2 cases in which the blood-culture was negative, the post-mortem signs of septicaemia were present, and in the remaining 1, which had been included in this group for convenience and was the only 1 of the

6 fatal cases in which a post-mortem examination was not carried out, there were clinical signs of general peritonitis, although an operation was not performed.

Of the 4 cases which recovered, 2 subsided without any complication developing, the third developed a moderate degree of pelvic cellulitis which quickly subsided, and the fourth developed a white leg and an extensive pelvic cellulitis which slowly subsided without active treatment.

The 6 fatal cases would now be considered separately. The first was a case of septicaemia with a scarlatiniform rash; the patient died within 48 hours of admission. Probably insufficient doses of protonsil were given not soon enough after admission; only 140 c.c. were given by injection, and the few tablets given by mouth were vomited.

The second case of septicaemia followed an abortion; the patient lived 8 days after admission; only 90 c.c. of prontosil were given, with 3.6 grains by mouth. Post-mortem examination showed small pyaemic abscesses in the lungs.

The third patient had septicaemia and peritonitis; she died within 37 hours after admission; 80 c.c. of prontosil were given, with 3.7 grains by mouth, but this treatment was not commenced till 15 hours after admission. Operation should also have been carried out in this case.

The fourth case was one of pelvic abscess with septicaemia following an accidental haemorrhage; the patient lived for 49 days after admission. The abscess was incised; 1,390 c.c. and 168 grains of prontosil were given by mouth. The patient improved and seemed likely to recover, but a relapse occurred. Post-mortem examination showed that the pelvic sepsis had almost completely resolved, but the inferior vena cava and its tributaries were full of septic clot.

The fifth case was one of delayed chloroform poisoning, following a difficult forceps delivery of a stillborn child. A small dose of prontosil was given on admission, but it was considered wiser to discontinue the use of this drug on account of jaundice. The signs suggested general peritonitis, but operation was not carried out. A post-mortem examination was not obtained.

The final case was admitted only two days after normal delivery, with a very virulent infection, the source of which was probably an abscess of the neck in each of two children of the patient. Operation was carried out, and generalized peritonitis was found, but the patient died 7 hours after admission. The interesting fact about this patient was that prontosil was given by mouth and by injection, 4 hours before operation, and though film examination showed the peritoneal exudate to be full of streptococci and culture was made immediately, no organisms were grown. A feebly growing haemolytic streptococcus was found in blood-culture, but it was not found possible to isolate this from a contaminating staphylococcus. These findings would strongly indicate that prontosil has a bactericidal effect on the organism *in vivo*.

Comment. In reviewing these cases, it could be seen that altogether there were 9 deaths out of 53 cases, a mortality of 17 per cent; or, considering only the infections due to a haemolytic streptococcus, 6 deaths out of 30 cases, a mortality of 20 per cent. He could not give the previous mortality at Walton Hospital for all cases of haemolytic streptococcal infection, but

Colebrook and Kenny stated that the mortality at Queen Charlotte's Hospital for the 5 years before the introduction of prontosil was between 16.6 per cent and 31.6 per cent; Dr. Dora Colebrook quoted figures from the literature ranging between 21 per cent and 37.5 per cent. These were, of course, the figures of the mortality of cases which were sufficiently serious to be admitted to special hospitals for treatment, rather than the figures of the mortality of all haemolytic streptococcal cases, many of which were undoubtedly mild. In comparing these figures with those published recently giving the results of treatment with prontosil, he found that Colebrook and Kenny reported a mortality of 4.7 per cent in 64 cases; Foulis and Barr a mortality of only 1.4 per cent in 70 cases, although in only 18 of these was a haemolytic streptococcus found. It would thus be seen that on the surface there was not any striking reduction in mortality in the present series. When, however, the 6 deaths are individually considered, it is found that 2 of the patients were gravely ill on admission with peritonitis, and died 7 and 37 hours respectively after admission. Both of these had, in addition, septicaemia; according to Colebrook and Kenny, and also in view of his own experience at Walton, this complication was almost invariably fatal prior to the introduction of prontosil. In 2 other cases, probably inadequate doses were given in the light of our present knowledge, and 1 patient was gravely ill with toxic jaundice. Considering septicaemia alone, and including 1 case of peritonitis without septicaemia, he found that the mortality was 60 per cent in 10 cases In going through the records of Walton Hospital for 1934, 1935, and 1936, prior to the introduction of prontosil, he found that among 36 cases of septicaemia, peritonitis, or both, which were proved by blood-culture, operation or post-mortem examination, the mortality was 86 per cent. In 25 cases of non-pelvic septicaemia, the mortality was 92 per cent. One other important factor had to be considered, and that was that the dosage used had been small compared with that which had been recommended elsewhere. Thus the average dose given to the third group of general infections had been only 325 c.c. and 41 grains; or, excluding the 1 case in which the dose was very large, 107 c.c. and 23 grains. He felt that one or two of these patients might have been alive now had bigger doses been given. On the whole he was not prepared to draw very emphatic conclusions as to the value of these drugs in the treatment of puerperal sepsis. He thought there could be no question that the temperature fell, the condition of the patient improved, the resistance was raised, and the incidence of serious complications was reduced if these drugs were used. In any case of established infection, the evidence in their favour was sufficiently strong for them to be given early in large doses while bacteriological examination was being carried out. They could do no harm and valuable time might be saved.

The great tragedy about these drugs seemed to be that they had been introduced into practice without adequate clinical controls, and now that they seemed to have been so dramatically successful, no one had the courage not to use them. There seemed to be strong evidence that the virulence of puerperal sepsis was decreasing, and evidence had been brought forward in favour of this from London and Sheffield. On reading the records of septic patients at Walton Hospital back to 1934, his impression was that there had been a fall in both the incidence and virulence of puerperal sepsis since that date.

Experiments in prophylaxis. Dr. Williams explained that each alternate case of the same operative procedure had been given prontosil, and the other cases used as controls. As patients were delivered in three different parts of the hospital, it had been difficult at times to preserve this strict alternation, and, therefore, there were a few more cases in the control series. No attempt had been made to select cases; no contra-indication to the drug had been recognized until recently, when it had been thought inadvisable to give it to patients with toxaemia who had recently been treated with intravenous magnesium sulphate, which was the routine treatment of severe toxaemia at Walton Hospital. In a few cases, such as cases of Caesarean section, the drug had been given shortly before delivery, but in most cases it had been given in the third stage of labour or shortly after delivery; this had been easy to do at Walton Hospital because in most abnormal cases delivery was carried out under spinal anesthesia. The drug had then been continued for a week in doses of three tablets of 0.3 grain three times daily. Each patient had thus about 63 tablets, or 19 grains, of the drug. The administration of the drug was daily noted on the chart. A 4-hourly temperature chart had been kept throughout the patient's stay in hospital, except in a few cases in which it was kept only for a week. It had been thought interesting to compare the morbidity as read by the different standards in use. There was, unfortunately, no generally accepted and used standard of maternal morbidity in this country at the present moment. It seemed, on the whole, that the exact standard was immaterial so long as it was accurately defined and generally used.

The total morbidity of the whole 302 cases had been considered (a single rise of temperature to 100°F., or any two rises to 99°F., excluding the first 24 hours after delivery), together. By the arbitrary standard he had used it was seen to reach the high figure of 71 per cent. On the British Medical Association's standard it was 26 per cent on a 4-hourly chart, and 16 per cent on a 12-hourly chart. By the Ministry of Health's standard it was 17 per cent on a 4-hourly chart, and 12 per cent on a 12-hourly chart. Taking the Ministry of Health's standard to mean any two rises to 100.4°F., it was found that the figures rose to 22 per cent and 16 per cent, which thus approximated to the Ministry of Health's figures. He had tried to ascertain the effect of the temperature during the first 24 hours on the figures, but, as in many cases the 4-hourly charts were not complete for the whole 24 hours, this had not been possible.

The main conclusion to be drawn from this would seem to be that there was a considerable difference in readings between a 4-hourly and a 12-hourly chart.

The results. Details of the cases were shown in Table III. In some cases, of course, more than one operative procedure had been carried out, and such cases had come under the heading of only one operation, usually the most important one. The perineal repairs had all required extensive suture under a general or spinal anaesthetic; small lacerations had not been included.

The findings, as regards morbidity, are shown in Table IV, and the figures are reduced to percentages for purposes of comparison. There was one death, from cardiac failure due to mitral stenosis, which occurred in the prontosil series, and this would be mentioned in the discussion on toxicity. On the whole, it would seem that there was little difference in the incidence of

morbidity between the two series, by the standards used in this table, although the figures in the prontosil series were slightly higher. The rates of morbidity, when judged by the commonly used standards, were high, but it must be remembered that many serious cases were included in the series, such as failed forceps, severe toxaemia, and antepartum haemorrhage. The number of cases in which there was definite evidence of pelvic infection and of pyelitis had been stated. The only 4 cases of serious sepsis occurred in the control series. There were 2 cases of septicaemia, both mild, due, respectively, to the staphylococcus aureus and the bacillus coli; there was 1 case of pelvic peritonitis and cellulitis, and one rather obscure case of sterile peritoneal effusion followed by acute pancreatitis. The patient was treated with prontosil and recovered. The neonatal deaths were higher in the prontosil series, but there were not any that could not be explained by accidents of labour or pregnancy. The number of cases of neonatal sepsis which had taken the form of cutaneous infection in the babies had been the same in both series.

The main type of organism found in lochial swabs is shown in Table V. It will be seen that 49 swabs were taken in the prontosil series and 35 swabs in the control series. It can also be seen that in the control series, haemolytic streptococci were isolated, usually in pure culture, in 6 cases, but in no case in the prontosil series, although the number of cultures taken was considerably larger. Non-haemolytic streptococci and the staphylococcus aureus were more frequent in the prontosil series, but the bacillus coli was less frequent.

Toxic effects. The possibility of toxic effects occurring with a new drug was obviously of some importance. These were found to be very rare with the septic cases treated, but seemed to have been more frequent and disturbing with the prophylactic cases. There had been only 1 death, and this was in a patient admitted during pregnancy with advanced cardiac failure from mitral stenosis. Her condition improved with treatment, and during labour the forceps was applied when the head was low. Prontosil was given prophylactically, but as signs of cardiac failure recurred with cyanosis, it was discontinued after a few days. Death occurred 10 days after delivery. A post-mortem examination was not obtained, but there seemed to be no doubt that death was due to cardiac failure from valvular disease.

Vomiting had occurred in a few cases shortly after delivery, but gastric disturbances had not otherwise been noted. No signs of renal irritation had been observed, but routine catheter specimens had not been examined.

The only disturbing feature had been cyanosis. In the earlier cases this occurred only occasionally, and its significance was not appreciated, but recently it seemed to have been becoming more frequent. Altogether some degree of cyanosis had occurred in 23 cases, or 16 per cent. Its explanation was somewhat difficult. Altogether, spectroscopic examination of the blood had been carried out in the 8 cases which had occurred, and in no case had sulphaemoglobin been found. In one case methaemoglobin had been found, and it is probable that it was present in some of the others, but was not looked for. In only 1 case was cyanosis persistent, and in this case magnesium sulphate had been given; the blood was not examined in this case. In all the other cases it had passed off quickly without ill-effect. It had occurred most frequently in the first few days in primiparae with a torn perineum or after episiotomy, and it was possible that constipation was an important

factor. As has recently been shown, methaemoglobinaemia was probably more important than sulphaemoglobinaemia. The only danger was when a patient developed sulphaemoglobinaemia in the presence of severe anaemia. Only 1 death was said to have been due to this, that reported by Frost in 1937; on reading through the rather meagre details in the clinical and post-mortem report of this case, Dr. Williams thought there was little evidence that the death was due to sulphaemoglobinaemia rather than to septicaemia.

Summary. What conclusions could be drawn from these findings? It had been shown that there was little difference in the incidence of sepsis in the two series, though all the serious cases had occurred in the control series. The main difference, however, would appear to be in the finding that in no case receiving prontosil had a haemolytic streptococcus been isolated. Could we conclude from this that prontosil protected against infection with haemolytic streptococci? The evidence seemed to be in favour of this. Though all the control cases which were infected with haemolytic streptococci were mild cases, it seemed reasonable to suppose that the haemolytic streptococcus was responsible for infection in them. It was true that streptococci found had not been typed in accordance with modern bacteriological practice, but Professor Hedley Wright had now arranged to have this done, and the only organism examined so far, the last one isolated in the series, had proved to be of the pathogenic variety.

If indeed we could protect patients against infection with haemolytic streptococci, it might be said to be revolutionary, and perhaps the biggest advance in obstetrics since the days of Semmelweiss. Statistics showed that the haemolytic streptococcus was found in 36 per cent to 88 per cent of septic cases admitted to hospital, and was responsible for between 71 per cent and 96 per cent of the deaths. It was responsible for the epidemics which still occurred in even the best run institutions, for most of the serious complications of the puerperium, prolonged illnesses, and for those tragic fulminating cases which occurred after normal labour.

We now knew definitely that the infecting organism came from one of two sources, either from a streptococcal infection in the neighbourhood, or from the respiratory tract of an attendant. Our first line of defence must always be to prevent infection reaching the patient, and in ordinary circumstances this was sufficient protection. Thus at Walton Hospital during the last 18 months, in approximately 4,000 deliveries, there had not been one cases of septicaemia, peritonitis, or serious infection due to a haemolytic streptococcus, in spite of considerable overcrowding and the use of large wards. With the best of care, however, patients might become infected, and it was then that drugs such as these new ones might be of value. Their introduction might only be a tragedy, however, if they were to lead to neglect of sound obstetric technique and an increased amount of interference.

It was now nearly a quarter of a century since the discoverer of salvarsan made the prophecy that within a few years we should be able successfully to treat bacterial diseases by chemotherapeutic methods. Perhaps that day was only just now dawning, and if it did a new era would be opened in obstetrics and medicine similar to that opened in surgery by Lister.

Discussion. The discussion on this paper was postponed until the autumn meeting in Liverpool.

TABLE I.

Results of treatment with prontosil.

	Total	Deaths
Cases not infected with haemolytic streptococci	23	3

Cases infected with haemolytic streptococci:

	GROUP 1 Infection localized to perineum, vagina and uterus	GROUP 2 Infection involving pelvic cellular tissue, peritoneum, veins on Fallopian tubes and ovaries	GROUP 3 Septicaemia and peritonitis
Number of cases	13	7	10
Deaths	0	0	6
Complications ...	2*	0	1†

Total mortality	9 deaths in 53 cases = 17 per cent
Mortality of cases infected with haemolytic streptococci	6 deaths in 30 cases = 20 per cent
Mortality of septicaemia	6 deaths in 9 cases = 67 per cent
Mortality of puerperal septicaemia at Walton Hospital during 1934, 1935, and 1936 (prior to the introduction of prontosil)	26 deaths in 30 cases = 87 per cent
Mortality of non-pelvic septicaemia for 1934, 1935, and 1936	23 deaths in 25 cases = 92 per cent

* Pelvic cellulitis 1; phlebitis of leg 1. † Pelvic cellulitis.

TABLE II.

Cases of Septicaemia and Peritonitis.

	Delivery	Lesion	Blood-culture	Treatment	Prontosil		Duration		Result
					c.c.	tablets			
1.	Normal	Septicaemia	Negative	—	140	8	42	hours	Died
2.	Normal	Septicaemia	Positive	—	65	56	48	days	Good
3.	Abortion	Septicaemia	Positive	—	90	12	8	days	Died
4.	Normal	Septicaemia	Positive	—	200	102	25	days	Good
5.	Normal	Septicaemia	Positive	—	196	244	61	days	Good; cellulitis; white leg
6.	Abortion; ischio rectal abscess	Septicaemia	Positive	Incision	115	180	30	days	Good
7.	Normal	Septicaemia and peritonitis	Positive	—	80	9	37	hours	Died
8.	Accidental haemorrhage	Pelvic abscess and septicaemia	Positive	Incision	1390	594	48	days	Died
9.	Forceps	Peritonitis and acute yellow atrophy?	Negative	—	20	9	4	days	Died
10.	Normal	Septicaemia and peritonitis	Positive	Drainage	60	8	7	hours	Died

TABLE III.

Prophylactic experiments.

	Cases receiving prontosil	Control cases
Forceps (including craniotomy)	40	46
Episiotomy and perineal repair	61	74
Breech delivery	10	10
Caesarean section	7	10
Artificial ruptures of the membranes ...	7	7
Manual removal of the placenta	4	4
Version during labour	8	8
Induction with a stomach-tube	3	5
Total	140	162

TABLE IV.

Results of prophylactic experiments.

	Prontosil series	Control series
Total	140	162
Deaths	1	0
Morbidity: new standard	101 = 72 per cent	114 = 70 per cent
British Medical Association's standard	34 = 24 per cent	45 = 28 per cent
Ministry of Health's standard	23 = 16 per cent	29 = 18 per cent
Pelvic infection	14 = 10 per cent	15 = 9 per cent*
Pyelitis	10 = 7 per cent	7 = 4 per cent
Stillbirths	19 = 14 per cent	18 = 11 per cent
Neonatal deaths	10 = 7 per cent	6 = 4 per cent
Neonatal sepsis	2	2
Cyanosis	23 = 16 per cent	—

* Bacillus coli septicaemia, staphylococcus aureus septicaemia, pelvic peritonitis and cellulitis, peritoneal effusion and pancreatitis.

TABLE V.

N-Organisms Isolated.

	Prontosil cases	Control cases
Number of lochial swabs	49	35
Haemolytic streptococci	0	6
Non-haemolytic streptococci	5	3
Staphylococcus aureus	7	2
Bacillus coli	11	15

TABLE VI.

Comparison of standards of maternal morbidity.

Total cases	302
New standard	215 cases = 71 per cent
British Medical Association's standard on a 4-hourly chart	79 cases = 26 per cent
British Medical Association's standard on a 12-hourly chart	47 cases = 16 per cent
Ministry of Health's standard on a 4 hourly chart	52 cases = 17 per cent
Ministry of Health's standard on a 12-hourly chart	36 cases = 12 per cent
Public Health standard, meaning any 2 rises to 100.4°F. on a 4-hourly chart	66 cases = 22 per cent
Public Health standard, meaning any 2 rises to 100.°F. on a 12-hourly chart	47 cases = 16 per cent

Mr. T. F. TODD (Manchester) read a short paper on

THE RELIEF OF PAIN IN PELVIC MALIGNANT DISEASE.

In the course of his remarks Mr. Todd said that he had obtained very good results from the intrathecal injection of 1.5 c.c. of alcohol. In order to get above the nerve roots concerned, the injection usually had to be made between the twelfth dorsal and the first lumbar vertebra.

DISCUSSION.

Professor FARQUHAR MURRAY (Newcastle) said that in one of his cases treated by this method incontinence of urine and faeces had occurred.

Mr. HARVEY EVERS (Newcastle) said that he was obtaining good results from pre-sacral sympathectomy.

Professor FARQUHAR MURRAY (Newcastle) read a paper on

THE EVOLUTION OF THE EMERGENCY SERVICE.

He emphasized the need for expert advice being at the disposal of the doctors in industrial practice as an essential prelude to the emergency service. Some emergencies were spontaneous and unexpected, but a number resulted from the absence of organized medical care and of the expert advice and operative skill being at the disposal of doctors called to deal with abnormal conditions.

A practical demonstration was given by sending an emergency call to the maternity hospital, which was 1 mile away. Within 10 minutes a nurse arrived in the lecture hall with the emergency outfit contained in one large tin, a drum, a package, and one or two oddments.

He concluded by giving details of the scale of fees which prevailed, and strongly advised the formation of a panel of consultants at the disposal of the doctors.